36. (Amended) An isolated nucleic acid molecule encoding a receptor protein tyrosine kinase (rPTK) having amino acid sequence SEQ ID NO:8.

39. (Amended) A method for preparing a receptor protein tyrosine kinase (rPTK) having amino acid sequence SEQ ID NO:8 comprising culturing the host cell of Claim 36 expressing said amino acid sequence SEQ ID NO:8 and recovering said amino acid sequence SEQ ID NO:8 from the host cell culture.

41. (Amended) An isolated nucleic acid molecule which hybridizes to a nucleic acid molecule encoding amino acid sequence SEQ ID NO:8 and complements thereof.

42. (Amended) An isolated nucleic acid molecule which hybridizes to a nucleic acid molecule having nucleic acid sequence SEQ ID NO:7 and complements thereof.

43. (Amended) An isolated nucleic acid molecule which hybridizes to a nucleic acid molecule encoding amino acid sequence SEQ ID NO:4 and complements thereof.

44. (Amended) An isolated nucleic acid molecule which hybridizes to a nucleic acid molecule having nucleic acid sequence SEQ ID NO:3 and complements thereof.

REMARKS

Claims 41 and 43 have been amended to correctly identify the amino acid sequences. Additionally, Claims 31, 34, 36, 39 and 41-44 have been amended to more accurately define the present invention. No question of new matter arises and entry of the amendments is respectfully requested.

Claims 31-44 are before the Examiner for consideration.

Rejection under 35 U.S.C. §101

The Office Action rejects Claims 31-44 under 35 U.S.C. § 101. In particular, the Office Action asserts:

> It is clear from the instant specification that HPTK6 is what is termed an "orphan receptor" in the art. This is a protein whose cDNA has been isolated because of its similarity to known proteins. There is little doubt that, after complete characterization, this protein will probably be found to have a patentable utility. This further characterization, however, is part of the act of invention and until it has been undertaken Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 USPQ 689 (Sup]. Ct., 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 USC § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility...
>
> The instant claims are drawn to an isolated nucleic acid encoding a protein of as yet undetermined function or biological significance, as indicated by the text in lines 16-19 on page 7 of the instant specification. There is absolutely no evidence of record or any line of reasoning that would support a conclusion that a protein of the instant invention is associated in any way with the plurality of causally unrelated disorders that are listed on page 63 of the instant specification. Until some actual and specific significance can be attributed to the protein identified in the specification as HPTK6, or the gene encoding it, the instant invention is incomplete. The protein encoded by a DNA of the instant invention is a compound known to be structurally analogous to proteins which are known in the art as receptor tyrosine kinases. In the absence of a knowledge of the natural ligands or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which inhibit or induce its activity is clearly to use it as the object of further research which has been determined by the courts to be a utility which, alone, does not support patentability. The

> employment of a protein of the instant invention, or a nucleic acid encoding that protein, as a tissue specific marker as suggested by the text on page 63 of the instant application is not a substantial or a specific utility. All human proteins can invariably be classified into two categories, those which are expressed in a tissue or developmentally specific manner and those which are expressed ubiquitously. It can be alleged that any protein which is expressed in a tissue specific manner can be employed to detect the tissue in which it is expressed in a sample. Alternately, a human protein which is expressed ubiquitously can be employed to detect the presence of any human tissue in a sample. Such utilities are analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific or substantial utility.

Applicants respectfully traverse the rejection.

Whether a disclosure is sufficient to meet the practical utility requirement of 35 U.S.C. § 101 requires resolution of the following issues: (1) What utility is disclosed? (2) Does the stated utility comply with the "practical utility" requirement of 35 U.S.C. §101, as delimited by prior decisions of the judiciary? [and] (3) Does the disclosure contain sufficient disclosure to meet the how-to-use requirement of 35 U.S.C. §112, first paragraph, with respect to the stated utility? Cross et al. v. Iizuka et al., 224 USPQ 739 (Fed. Cir. 1985).

"[T]he proofs of utility should be convincing to one skilled in the art... it is evident that the amount of evidence required depends on the facts of each individual case... [t]he character and amount of evidence needed may vary, depending on whether the alleged operation described appears to accord with or to contravene established scientific principles and beliefs." In re Walter E. Buting, 163 USPQ 689 (CCPA 1969).

In accordance with the Revised Interim Utility Guidelines (March 7, 2000), "[f]or product claims that do not recite any utilities, disclosure or assertion of one specific, substantial and

credible utility meets the criteria of 35 U.S.C. §101."[1] Applicants respectfully submit that the present disclosure coupled with the knowledge in the art provide a specific, substantial and credible utility for the claimed invention. The claimed invention is an isolated nucleic acid molecule encoding a receptor protein tyrosine kinase (rPTK) having amino acid SEQ ID NO:4 or SEQ ID NO:8 (independent Claims 31 and 36 respectively), an isolated nucleic acid molecule that hybridizes to a nucleic acid molecule encoding amino acid SEQ ID NO:8 or SEQ ID NO:4, (Claims 41 and 43 respectively), and an isolated nucleic acid molecule that hybridizes to a nucleic acid molecule having nucleic acid SEQ ID NO:7 or SEQ ID NO:3 (Claims 42 and 44 respectively) (the present specification discloses that the protein tyrosine kinase is HPTK6).

HPTK6 has been shown to have a patentable utility as evidenced by issuance of U.S. Patent No. 6,087,144. Further, page 63 and pages 77-78 of the specification disclose that HPTK6 may be useful to treat disease via stimulating cell growth and differentiation. The nucleic acid

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[1]The Utility Guidelines (in part) define specific, substantial and credible as follows:

> Specific utility" - A utility that is *specific* to the subject matter claimed...
>
> "Substantial utility" - A utility that defines a "real world use"...
>
> "Credible utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong." Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided.)...

The Utility Guidelines define "well-established utility" as follows:

> "Well-established utility" - A specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art...

encoding HPTK6 may be used as a diagnostic for tissue-specific typing. For example, *in situ* hybridization, Northern and Southern blotting, and PCR analysis may be used to determine whether DNA and/or RNA encoding rPTK is present in the cells being evaluated.

In addition, the isolated HPTK6 polypeptide encoded by the nucleic acid may be used in qualitative diagnostic assays and to produce antibodies which have specific, substantial, and credible uses. Pages 70-75 of the specification disclose that these HPTK6 antibodies may be used (1) as ligands to HPTK6, which can be used in diagnostic assays to, e.g., detect expression of HPTK6 in specific cells, tissues, or serum, such as by immunoassays, competitive assays, and sandwich assays, (2) in passively immunizing patients, and (3) to affinity purify HPTK6 from recombinant cell culture or from natural sources. The utilities described in the specification are specific and substantial.

Furthermore, the utilities described in the specification are credible. In particular, the disclosure in the specification is supported by numerous, more recent publications in the field. Some of the literature in this area is discussed below (copies of each of the references discussed below are attached for the Examiner's review).

1. Johnson et al., A receptor tyrosine kinase found in breast carcinoma cells has an extracellular discoidin I-like domain, Proc. Natl. Acad. Sci. USA, 90:5677-5681 (1993).

As disclosed in the present specification, HPTK6 is a receptor molecule that has a discoidin[2] domain. Several receptors having extracellular (discoidin) domain structures similar to HPTK6 have been isolated and described in the art. For example, Johnson et al. discloses a receptor tyrosine kinase found in breast carcinoma cells that has a discoidin domain. See

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[2]Discoidin is a lectin described during the cell aggregation process of the slime mold *Dictyostelium discoideum*. See Vogel, infra, at page S77.

Johnson et al., Figure 1. Johnson et al. discloses that the discoidin domain is a feature that may mediate specific interactions with similar ligands and that characterization of the ligand could reveal a set of interactions involved in multiple biological regulatory systems. See Johnson et al. at page 5680.

Further, Johnson et al. describe immunizing rabbits and making anti-discoidin domain receptor (DDR) antisera. (See page 5677, right hand column, lines 23-28). In particular, a fragment of the DDR cDNA was subcloned to pUR290 to form a fusion protein, which was then purified for rabbit immunization. (Id.) The DDR cDNA was also subcloned into a mammalian expression vector which was used to transfect COS-7 cells. These cells were then used in immunoblotting. (See page 5677, right hand column, lines 29-34). To characterize the DDR polypeptide, COS-7 cells were transfected with the DDR cDNA in a mammalian expression vector and reacted with the antisera described above. (See page 5679, paragraph bridging left and right hand columns). Thus, Johnson et al. show the use of a nucleic acid encoding an rPTK to form anti-rPTK antibodies and a real world utility for the antibodies. Furthermore, this type of use is described in the specification, e.g., at page 70, lines 31-33.

2. Vogel, Discoidin domain receptors: structural relations and functional implications, The FASEB Journal, 13:S77-S82 (1999).

Vogel is a review article on discoidin domain receptors. Vogel discusses the structural and functional similarities between known members of this tyrosine kinase receptor subfamily, which includes DDR, NEP, Cak, Ptk-3, TrkE, MCK-10, RTK6, EDDR1, NTRK4, CCK-2, Tyro-10 and TKT. See Vogel at page S77. In particular, Vogel states:

> During the search for tyrosine kinase proteins expressed in human malignancies, a novel subfamily of receptor tyrosine kinases (RTK) was discovered. This subfamily is distinct from other members of the large RTK group due to a homology domain to discoidin...

See Vogel at page S77.

> Five different studies have detected an overexpression of DDR1 in human tumors... Transcripts for DDR1 are found in highly invasive tumor cells, whereas transcripts for DDR2 are detected only in the surrounding stromal cells, suggesting an involvement of DDR1 and DDR2 in tumor progression.

See Vogel at page S78.

> The overexpression of DDR1 in several different human cancers suggest they function in tumor progression... Other human diseases with deregulated matrix production, including lung fibrosis, liver cirrhosis, osteoporosis, and rheumatoid arthritis may present aberrant DDR expression or signaling.

See Vogel at page S81.

Additional references disclose that receptors having extracellular (discoidin) domain structures similar to HPTK6 are expressed in cancer cell lines. See, for example, Sakuma et al., Receptor protein tyrosine kinase *DDR* is up-regulated by p53 protein, FEBS Letters, 398:165-169 (1996) (which discloses that the DDR gene is up-regulated by adenovirus-mediated p53 expression in SAOS2 carcinoma cell line); Perez et al., Identification and chromosomal mapping of a receptor tyrosine kinase with a putative phospholipid binding sequence in its ectodomain, Oncogene, 9:211-219 (1994) and Perez et al., Identification of two isoforms of the *Cak* receptor kinase that are co-expressed in breast tumor cell lines, Oncogene, 12:1469-1477 (1996) (which discloses Cak and expression of a form of Cak in breast tumor cell lines); Laval et al., Isolation and characterization of an epithelial-specific receptor tyrosine kinase from an ovarian cancer cell line, Cell Growth & Differentiation, 5:1173-1183 (1994) (which discloses the isolation of RTK6 from SKOV-3, an epithelial ovarian cancer cell line); Playford et al., The genomic structure of discoidin receptor tyrosine kinase, Genomic Research, 6:620-627 (1996) (which discloses that DDR has been isolated from various sources, including metastatic breast cancer lymph nodes,

breast cancer cell line MCF-7 and HeLa cell line); and DiMarco et al., Molecular cloning of *trk*E, a novel *trk*-related putative tyrosine kinase receptor isolated from normal human keratinocytes and widely expressed by normal human tissues, J. Biol. Chem., 268(32):24290-24295 (1993) (which discusses trkE).

Furthermore, Nemoto et al., Overexpression of protein tyrosine kinases in human esophageal cancer, Pathobiology, 65(4):195-203 (1997) (abstract attached), discloses that the observation of the expression of discoidin domain receptor tyrosine kinases in esophageal squamous cell carcinoma suggests that these receptors play an important role in the regulation and proliferation of esophageal cancer.

Perez et al. (Oncogene (1996) 12, 1469-1477) also describe real world uses for anti-rPTK antibodies prepared from rPTKs. In Perez et al., antibodies specific for Cak I and Cak II were prepared. (See page 1470, right hand column, lines 52-54). The antibodies were then used to analyze receptor expression and to analyze the abundance of Cak I and Cak II in adult and embryonic tissues. (See paragraph bridging pages 1470-1471 and page 1471, right hand column, lines 6-8). These diagnostic analyses are real world, credible, and substantial uses for anti-rPTK antibodies. Further, the type of analyses described in Perez et al. are described in the specification as uses of rPTK antibodies produced using the claimed nucleic acid. (See page 71 of the specification at lines 6-14).

Real world uses for anti-rPTK antibodies are also described by Laval et al. In Laval et al., polyclonal antisera were prepared in rabbits using thyroglobulin-conjugated synthetic peptides from the juxtamembrane and COOH-terminal region. (See page 1174, line 57- page 1176, line 1). This antisera was used to identify the protein encoded. (See page 1174, lines 57-58). Additionally, the antibodies were used to predict the molecular weight of a protein. (See page

1177, right hand column, last paragraph). These biochemical characterizations are clear, credible, and substantial real world uses of anti-rPTK antibodies. (See the specification at, e.g., page 70, lines 31-33).

The references cited above confirm that discoidin domain receptors, such as HPTK6, are involved in cell growth and differentiation. Additionally, antibodies produced from the rPTKs encoded by the nucleic acid (such as the nucleic acid molecules presently claimed) have credible and substantial real world uses. Thus, based on the disclosure in the specification and the disclosures in the references discussed above, it is clear that the isolated nucleic acid molecules encoding an HPTK6 receptor such as the nucleic acid molecules claimed in Claims 31 and 46 meet the statutory utility requirements. Accordingly, reconsideration and withdrawal of the rejection of Claims 31-44 under 35 U.S.C. § 101 are respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph

The Office Action rejects Claims 31-44 under 35 U.S.C. §112, first paragraph as failing to adequately teach how to use the instant invention for those reasons given in the rejection under 35 U.S.C. §101 set forth above.

Applicants respectfully traverse the rejection.

A deficiency under 35 U.S.C. §101 also creates a deficiency under 35 U.S.C. §112, first paragraph. In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); In re Kirk, 376 F.2d 936, 942, 153 USPQ 48, 53 (CCPA 1967). Thus, in order to be enabled, a claim must be supported by a disclosure showing practical utility. As discussed above, the present disclosure coupled with the knowledge in the art provide a specific, substantial and credible utility for the claimed invention. Thus, the claimed invention meets the requirements of 35 U.S.C. §112, first

paragraph. Reconsideration and withdrawal of the rejection of Claims 31-44 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejections under 35 U.S.C. §112, second paragraph

1. On page 5 of the Office Action, Claims 31-40 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Office Action asserts that the instant specification does not identify that property or combination of properties which is unique to and definitive of a "HPTK6 receptor protein tyrosine kinase". As a result, an artisan cannot determine if a compound which meets all of the other limitations of the claim would then be included or excluded from the claimed subject matter by the presence of this limitation.

In response, Applicants have amended the claims to exclude the recitation of "HPTK6". Applicants submit that as amended, the claims are sufficiently definite and respectfully request that the Examiner reconsider and withdraw this rejection.

2. On page 5 of the Office Action, Claims 41-44 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Office Action asserts that the limitation "stringent conditions" is conditional and the conditions under which this property is to be determined are not recited in the claims or in the instant specification.

In response, Applicants have amended the claims to remove the phrase "stringent conditions". Applicants submit that the amended claims are sufficiently definite and respectfully request that this rejection be reconsidered and withdrawn.

3. On page 6 of the Office Action, Claims 41 and 43 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Office Action states that there is no basis for a nucleic acid sequence in SEQ ID NO:4 or 8.

In response, Applicants have amended Claims 41 and 44 to properly recite that SEQ ID NO:4 and SEQ ID NO:8 are amino acid sequences. Applicants submit that these amended claims are sufficiently definite and respectfully request the reconsideration and withdrawal of this rejection.

Rejections under 35 U.S.C. §102(a)

Claims 31-44 are rejected under 35 U.S.C. §102(a) on page 6 of the Office Action as being clearly anticipated by Johnson et al. (PNAS 90:5677-5681, Jun. 1993). Additionally, Claims 31-33, 35-38, and 40-44 are rejected under 35 U.S.C. §102(a) as being clearly anticipated by Di Marco (J. Biol. Chem. 268:24290-24295, 15 Nov. 1993).

The Office Action states that the Declaration filed on May 1, 2000 under 37 C.F.R. §1.131 has been considered but is ineffective to overcome the Johnson et al. and DiMarco references because the declaration fails to show that Applicants had established a practical utility for a receptor protein tyrosine kinase of the instant invention or an isolated nucleic acid encoding such a receptor prior to the publication of these references.

Applicants submit that in the Declaration Under 37 C.F.R. §1.131 submitted with the previous Response, Applicants clearly demonstrated conception and reduction to practice of the claimed subject matter prior to the effective filing date of Johnson (June, 1993) and DiMarco (Nov., 1993). Further, Applicants submit that the claimed subject matter had a demonstrated specific and substantial utility by 1993 as defined by the Revised Interim Utility Guidelines and the Comments to the Utility Guidelines set forth in the Federal Register on Friday, January 5, 2001, and request full and favorable consideration of Declaration under 35 U.S.C. §1.131.

Applicants submit that by 1990, one skilled in the art knew that receptor protein tyrosine kinases can act as oncogenes. (See Gilardi-Hebenstreit et al., Oncogene (1992) 7, p. 2504, left column, third full paragraph). Thus, when the present invention was reduced to practice[3], it was already known in the art that receptor protein tyrosine kinases are involved in cell growth and differentiation. Accordingly, the receptor protein tyrosine kinase according to the present invention had an inherent utility at the time of reduction to practice based on an established utility for receptor protein tyrosine kinases and the homology between the present receptor protein tyrosine kinase and the class of protein tyrosine kinases generally. When a patent application claiming a nucleic acid asserts a specific utility, and bases the assertion upon homology to proteins or existing nucleic acids that have an accepted utility, the asserted utility must be accepted by the Examiner unless the Patent Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. (See Comments to the Utility Guidelines (Jan. 5, 2001) at Comment 19).

Notwithstanding the above, Applicants submit that a utility for the present invention was demonstrated in the Declaration under 37 C.F.R. §1.131 originally submitted on May 11, 2000. In this regard, Applicants respectfully direct the Examiner's attention to Exhibit A, which was submitted with the original Declaration. The ECD of the protein kinase (i.e., SEQ ID NO:8) was fused to IgG II to form a fusion protein. This fusion protein was used to make HPTK6 antibodies. (See, e.g., top of page 5 of Exhibit A). Thus, Applicants submit that another utility of the nucleic acid of the invention is to make a specific protein, which in turn is used to make specific antibodies, which, as discussed above, have well-known, credible, substantial, and specific uses.

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[3]Reduction to practice of a gene occurs when the gene has been isolated. (Fiers v. Revel, 25 USPQ2d 1601 (1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd , 18 USPQ2d 1016 (1991)).

In view of the above, Applicants submit that the isolated nucleic acid encoding a receptor claimed in Claims 31 and 36 had a specific, substantial, and credible utility before 1993 and that neither Johnson nor DiMarco are effective prior art references. Therefore, Applicants respectfully request that these rejections be reconsidered and withdrawn.

CONCLUSION

In light of the above, Applicants believe that this application is now in condition for allowance and therefore request favorable consideration.

If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

PIPER MARBURY RUDNICK & WOLFE

June 27, 2001
Date

Steven B. Kelber
Registration No: 30,073
Attorney of Record

Amy L. Miller
Registration No: 43,804

1200 Nineteenth Street, N.W.
Washington, D.C. 20036-2412
Telephone: (202) 861-3900
Facsimile : (202) 223-2085

SERIAL NO. 09/236,939

DOCKET NO.: 9491-018-27X DIV

MARKED-UP COPY OF AMENDED CLAIMS

31. (Amended) An isolated nucleic acid molecule encoding [an HPTK6] a receptor protein tyrosine kinase (rPTK) having amino acid sequence SEQ ID NO:4.

34. (Amended) A method for preparing [an HPTK6] a receptor protein tyrosine kinase (rPTK) having amino acid sequence SEQ ID NO:4 comprising culturing the host cell of Claim 33 expressing said amino acid sequence SEQ ID NO:4 and recovering said amino acid sequence SEQ ID NO:4 from the host cell culture.

36. (Amended) An isolated nucleic acid molecule encoding [an HPTK6] a receptor protein tyrosine kinase (rPTK) having amino acid sequence SEQ ID NO:8.

39. (Amended) A method for preparing [an HPTK6] a receptor protein tyrosine kinase (rPTK) having amino acid sequence SEQ ID NO:8 comprising culturing the host cell of Claim 36 expressing said amino acid sequence SEQ ID NO:8 and recovering said amino acid sequence SEQ ID NO:8 from the host cell culture.

41. (Amended) An isolated nucleic acid molecule which hybridizes [under stringent conditions] to a nucleic acid molecule [having nucleic acid] encoding amino acid sequence SEQ ID NO:8 and complements thereof.

42. (Amended) An isolated nucleic acid molecule which hybridizes [under stringent conditions] to a nucleic acid molecule having nucleic acid sequence SEQ ID NO:7 and complements thereof.

43. (Amended) An isolated nucleic acid molecule which hybridizes [under stringent conditions] to a nucleic acid molecule [having nucleic acid] encoding amino acid sequence SEQ ID NO:4 and complements thereof.

44. (Amended) An isolated nucleic acid molecule which hybridizes [under stringent conditions] to a nucleic acid molecule having nucleic acid sequence SEQ ID NO:3 and complements thereof.

#14 attachment
09/236939

Cross et al. v. Iizuka et al., 224 USPQ 739 (CA FC 1985)

Cross et al. v. Iizuka et al.

(CA FC)
224 USPQ 739

Decided Jan. 28, 1985
No. 84-1111
U.S. Court of Appeals Federal Circuit

Headnotes

PATENTS

1. Patentability -- Utility (§ 51.75)

Board did not err in finding that in vitro utility disclosed in foreign priority application is sufficient to establish practical utility under 35 USC 101.

2. Patentability -- Utility (§ 51.75)

Rigorous correlation of pharmacological activity between disclosed in vitro utility and in vivo activity is not necessary where disclosure of pharmacological activity is reasonable based upon probative evidence.

3. Patentability -- Utility (§ 51.75)

35 USC 112 "how to use" requirement is satisfied, despite failure of disclosure to reveal dosages for novel compound per se, those skilled in art having had sufficient information at critical date to determine dosage for desired pharmacological activity.

Particular patents -- Imadazole Derivatives

Iizuka, et al., application, Imidazole Derivatives, award of priority over Cross et al., application, N-(Phenoxyalkyl) Imidazoles as Selective Inhibitors of the Thromboxane Synthetase Enzyme and Pharmaceutical Compositions Thereof, affirmed.

Case History and Disposition:

Appeal from Patent and Trademark Office Board of Patent Interferences.

Patent interference No. 100,650, between Peter E. Cross, et al., application, Serial No. 95,755, filed Nov. 19, 1979, and Kinji Iizuka, et al., application, Serial No. 68,365, filed Aug. 21, 1979. From decision awarding priority to party Iizuka, party Cross, et al. appeals. Affirmed.

Attorneys:
Rudolf E. Hutz, and Connoly, Bove, Lodge & Hutz, both of Wilmington, Del. (Thomas M. Meshbesher, Wilmington, Del., on the brief) for appellants.

Peter D. Olexy, and Sugrue, Mion, Zinn, MacPeake & Seas, both of Washington, D.C. (Thomas J. MacPeak, Washington, D.C., on the brief) for appellees.

Judge:
Before Kashiwa, Bennett, and Bissell, Circuit Judges.

Opinion Text

Opinion By:
Kashiwa, Circuit Judge.

This appeal is from the decision of the United States Patent and Trademark Office (PTO) Board of Patent Interferences (Board) awarding priority on the single phantom count to Iizuka, et al. (Iizuka), the senior party. We affirm.

Background

Interference No. 100,650 was declared on 20 April 1981 between application serial No. 68,365, for "Imidazole Derivatives," filed by Iizuka on 21 August 1979 and application serial No. 95,755, for "N-(Phenoxyalkyl) Imidazoles as Selective Inhibitors of the Thromboxane Synthetase Enzyme and Pharmaceutical Compositions Thereof," filed by Cross, et al. (Cross) on 19 November 1979. The single phantom count of the interference is directed to imidazole derivative compounds and reads as follows:

> A compound selected from the group consisting of an imidazole derivative of the formula *Graphic material consisting of a chemical formula or diagram set at this point is not available. See text in hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.*
>
> wherein R is a hydrogen atom or an alkyl group having 1 to 6 carbon atoms, each of A_1 or A_2, which may be the same or different, are alkylene having 1 to 8 carbon atoms, m is 0 or 1, X is oxygen or sulfur, and each of R_1 or R_2, which may be the same or different, is a hydrogen atom *or an alkyl group having 1 to 6 carbon* atoms; R_3 is H, C_1-C_4 alkyl, C_1-C_4 alkoxy or halogen; and the pharmaceutically acceptable salts thereof. [1]

The applications of Cross and Iizuka both disclose inventions directed to imidazole derivative compounds which inhibit the synthesis of thromboxane synthetase, an enzyme which leads to the formation of thromboxane A_2 (TXA_2) [2] a highly unstable, biologically active compound which is converted to stable thromboxane B_2 by the addition of water. Thromboxane A_2, as of the time period during which the applications were filed, was postulated to be a causal factor in platelet

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aggregation. [3] Platelet aggregation is associated with several deleterious conditions in mammalia, including humans, such as platelet thrombosis, pulmonary vasoconstriction or vasospasm, inflammation, hypertension, and collagen-induced thrombosis.

Pursuant to 37 C.F.R. §1.231(a)(4) each party moved to be accorded the benefit of a foreign priority application under 35 U.S.C. §119, Cross claiming priority based upon a British application filed 13 December 1978, and Iizuka claiming priority based upon a Japanese application filed 21 August 1978. Each party opposed the motion of the other party, each party contending that the other party's foreign priority application did not comply with the disclosure requirements of 35 U.S.C. §112.

The primary examiner granted each party's motion, noting that the utility alleged in each application was of a pharmacological nature, i.e., the inhibition of thromboxane synthetase, and that inasmuch as the single phantom count of the interference was directed to a compound, it was not necessary that utility be established by tests and dosages with respect to human beings. The examiner found that one of ordinary skill in the art would know how to use the imidazole derivatives, i.e., be able to determine specific dosages, for biological purposes. Based upon the filing dates of the foreign priority applications, [4] Iizuka was declared the senior party and a show cause order was issued against Cross.

Cross requested a final hearing on the issue of the sufficiency of the Japanese priority application of Iizuka, and moved for a testimony period to present evidence on this issue. A testimony period was granted over the opposition of Iizuka, and Cross took the testimony of his expert witness, Dr. Smith, and Iizuka took the testimony of his expert witness, Dr. Ramwell and also proferred several exhibits pursuant to 37 C.F.R. §1.282. All testimony and exhibits related to the sufficiency of Iizuka's Japanese priority application, i.e., whether it complied with the disclosure requirements of 35 U.S.C. §112.

Decision of the Board

The Board noted that the sole issue before it was whether Iizuka was entitled to the benefit of his Japanese priority application. [5] Relying on In re Bundy, 642 F.2d 430, 209 USPQ 48 (CCPA 1981), and Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881 (CCPA 1980), the Board held that tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use. The Board found that the Japanese priority application disclosed pharmacological activity in the similar activity of the imidazole derivatives of the count to imidazole and 1-methylimidazole, which possess an inhibitory action for thromboxane synthetase, and that practical utility was disclosed in the strong inhibitory action for thromboxane synthetase from human or bovine platelet microsomes, i.e., an in vitro utility. [6]

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The Board further found that the Japanese priority application disclosed "how-to-use" knowledge directed to the practical utility in a microsome system, and that microsome assays were admittedly known in the art. A skilled worker could determine the relative strength of the imidazole compounds of the count vis-a-vis the known parent imidazole and 1-methylimidazole compounds for use in the microsome assay milieu. Knowledge of the pharmacological activities of compounds is beneficial to the medical profession, and requiring Iizuka to have disclosed in vivo dosages in the Japanese priority application would delay and frustrate researchers by failing to provide an incentive for early public disclosure of such compounds, thereby failing to further the public interest.

Accordingly, the Board held that the Japanese priority application contained an adequate how-to-use disclosure for the practical utility stated therein.

Issues

Whether the Board erred in finding that the utility disclosed in the Japanese priority application is sufficient to meet the practical utility requirement of 35 U.S.C. §101.

Whether the Board erred in finding that the Japanese priority application contained sufficient disclosure to satisfy the enablement, i.e., how-to-use, requirement of 35 U.S.C. §112. [7]

Opinion

Proper resolution of the issues before this court necessitates that we address, seriatim, the following questions: (1) What utility is disclosed by the Japanese priority application? (2) Does this stated utility comply with the "practical utility" requirement of 35 U.S.C. §101, as delimited by prior decisions of the judiciary? [8](3) Does the Japanese priority application contain sufficient disclosure to meet the how-to-use requirement of §112 with respect to the stated utility?

It is axiomatic that an invention cannot be considered "useful," in the sense that a patent can be granted on it, unless substantial or practical utility for the invention has been discovered and disclosed where such utility would not be obvious. Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). Where a constructive reduction to practice is involved, as contrasted to an actual reduction to practice, a practical utility for the invention is determined by reference to, and a factual analysis of, the disclosures of the application. Kawai v. Metlesics, 480 F.2d 880, 178 USPQ 158 (CCPA 1973).

1. Japanese Priority Application

The Board factually analyzed the Japanese priority application and found that the only effective disclosure relating to a stated utility for the imidazole derivative compounds of the phantom count was the following:

> [The compounds disclosed] are useful for treatment of inflammation, thrombus, hypertension, cerebral apoplexy, asthma, etc.
>
> Up to this time, it is a known fact that imidazole and 1-methylimidazole posses an inhibitory action for thromboxane synthetase and inhibit a biosynthesis of thromboxane A_2. (Prostaglandins, Vol. 13, pages 611-1977). However, since their inhibitory effect is not satisfactory one, these compounds have not been put to practical use yet as therapeutical medicines for diseases caused by thromboxane A_2, such as inflammation, hypertension, thrombus, cerebral apoplexy, asthma, etc.
>
> To develop some compounds possessing a strong inhibitory action for biosynthesis of thromboxane A_2, the present inventors devoted themselves to study for various imidazole derivatives, and as a result, found that the compounds [of this invention] possess a strong inhibitory action for
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> thromboxane synthetase from human or bovine platelet microsomes and are extremely useful as therapeutically active agents for diseases caused by thromboxane A_2, for example, inflammation, hypertension, thrombus, cerebal apoplexy, asthma, etc., and thus were proposed this invention based upon those findings.
>
> The imidazole derivatives * * * of this invention are novel compounds which are not described in literature, and which possess a strong inhibitory action for thromboxane synthetase from human or bovine platelet microsomes, and which exhibit a strong inhibitory action for biosynthesis of thromboxane A_2 in mammalia including human. In general, a satisfactory inhibitory effect is found at a level of molar concentrations of 2.5×10^{-8}, for example, 2-[p-(1-imidazolylmethyl)phenoxy]-acetic acid hydrochloride produce the about 50% inhibitory effect at the molar concentrations of 2.5×10^{-8}. Accordingly, the imidazole derivatives of this invention are extremely useful as therapeutical medicines for diseases caused by thromboxane A_2, such as inflammation, hypertension, thrombus, cerebral apoplexy, asthma, etc.

The Board found that these pertinent sections of the Japanese priority application disclosed some activity or utility, namely that the imidazole derivative compounds of the count possess a strong inhibitory action for thromboxane synthetase in human or bovine platelet microsomes. Cross' position is that the stated purpose or *sole* comtemplated utility of the invention of Iizuka is to provide a novel class of compounds which provide "practical use" as "therapeutical medicines for diseases caused by thromboxane A_2," and therefore the Board erred in its finding as to the stated utility of the Japanese priority application.

While recognizing that Kawai constrains an applicant to entitlement to the benefit of only what is disclosed in the foreign priority application and no more, we also recognize that foreign priority applications, as subsequently filed in the PTO, typically have a style and format dissimilar to the arrangement of application elements suggested by 37 C.F.R. §1.77. In part this arises because of differences in filing requirements in foreign patent offices, and in part because of the awkwardness resulting from direct literal translations from a foreign language to English. Thus, while the factual determination of the stated utility in an application prepared in the United States may be relatively straightforward, [9] the factual analysis of a foreign priority application to determine the utility disclosed therein may be more laborious and open to varying interpretations.

The weakness of Cross' position is that a fair reading of the pertinent sections of the Japanese priority application as set forth above, discloses utility for the imidazole derivative compounds of the phantom count both as an inhibiting agent for thromboxan synthetase in human or bovine platelet microsomes, as found by the Board, and as therapeutically active agents preventing the biosynthesis of thromboxane A_2, thereby functioning as a medicine preventing deleterious conditions caused by thromboxane A_2, as contended by Cross.

Evidence of any utility is sufficient when the count does not recite any particular utility. Nelson v. Bowler, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980). See also Rey-Bellet v. Englehardt, 493 F.2d 1380, 181 USPQ 453 (CCPA 1974); Knapp v. Anderson, 477 F.2d 588, 177 USPQ 688 (CCPA 1973); Blicke v. Treves, 241 F.2d 718, 112 USPQ 472 (CCPA 1957). Here the Board, which is charged with the factual determination of utility, [10] has found that the specification of the Japanese priority application disclosed a utility for the imidazole derivative compounds of the phanton count in the inhibition of thromboxane synthetase in human or bovine platelet microsomes. Inasmuch as the Board is charged with making this factual determination when the issue is raised, inasmuch as they have so done in the instant case, and inasmuch as there is credible evidence to support this factual determination, we are not prepared to say that the Board erred in its

finding as to the stated utility disclosed in the Japanese priority application.

2. Practical Utility

As noted in the preceding part of this opinion, Cross has contended that the Board erred in its finding as to the utility disclosed in the Japanese priority application. This argument may be viewed in a different perspective, we believe, which is that the stated utility in the Japanese priority application, as found by the Board -- the inhibition of thromboxane synthetase in human or bovine platelet microsomes [11] -- is not sufficiently correlated to a pharmacological activity [12] to be a practical utility. In other words, Cross may be arguing that the minimum acceptable level of utility disclosed in an application claiming a compound having pharmacological activity must be directed to an in vivo utility in order to comply with the practical utility requirement of §101.

The starting point for a practical utility analysis is Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). The Court in Brenner noted that "a simple, everyday word ["useful," as found in 35 U.S.C. §101] can be pregnant with ambiguity when applied to the facts of life." Id. at 529, 148 USPQ at 693. While noting that "one of the purposes of the patent system is to encourage dissemination of information concerning discoveries and inventions," id. at 533, 148 USPQ at 695, the Court found that a more compelling consideration in the determination of whether a patent should be granted "is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point -- where specific benefit exists in currently available form -- there is insufficient justification for permitting an applicant to engross what may prove to be a broad field." Id. at 534-35, 148 USPQ at 695. While we recognize that this case concerned a compound derived from a chemical process, we believe Brenner provides broad guidelines which are helpful in ascertaining what constitutes practical utility for compounds having a pharmacological effect.

In Nelson v. Bowley, 626 F.2d 853, 206 USPQ 881 (1980), our predecessor court, the Court of Customs and Patent Appeals, stated that "[k]nowledge of the pharmacological activity of any compound is obviously beneficial to the public" and concluded that "adequate proof of any such utility constitutes a showing of practical utility." Id. at 856, 206 USPQ at 883. [13] The tests [14] found by the court to be adequate proof of pharmacological activity or practical utility were a rat blood pressure (BP) test and a gerbil colon smooth muscle stimulation (GC-SMS) test. The BP test was an in vivo test, which was deemed by the court to be direct evidence as to the claimed activity, while the GC-SMS test was an in vitro test. [15]

The CCPA in Rey-Bellet v. Englehardt, 493 F.2d 1380, 1383, 181 USPQ 453, 454 (1974), stated that where a count contains no limitation related to utility, evidence establishing a substantial utility for any purpose is sufficient to show a reduction to practice. The court held that three in vivo tests [16] conducted in the United States prior to the filing of Englehardt's U.S. application failed to establish an actual reduction to practice. The court proceeded, however, to find sufficient evidence in the record to establish that Englehardt had conceived a utility for his compound prior to the filing date of his U.S. application. The evidence the court found to be sufficient was testimony by the inventor that he believed his compound would exhibit a particular pharmacological activity because of its structural similarity to anther compound which was known to possess the particular pharmacological activity. The court

found that the testimonial evidence of Englehardt was corroborated by two exhibits entered into evidence. The evidence adduced by Englehardt was found by the court to be sufficient proof that Englehardt had conceived that his compound had utility for the particular pharmacological activity prior to his U.S. filing date. The court further noted that this was a completed conception of utility because it appeared that nothing beyond the exercise of routine skill would have been required to demonstrate that Englehardt's compound possessed the particular pharmacological utility. While noting that the actual testing done was not sufficient to establish an actual reduction to practice, the court found that the extensive testing done in vivo on animals was routine in nature and was not, therefore, to be construed as an indicator that extensive research, i.e., inventive skill and/or undue experimentation, was required to resolve perplexing intricate difficulties related to the utilization of the compound for the particular pharmacological activity.

The CCPA in Kawai v. Metlesics, 480 F.2d 880, 178 USPQ 158 (1973), concurred with the finding of the Board that the applicants had failed to prove that their foreign priority application was adequate under the patent laws of the United States. The only disclosure in the foreign priority application relating to the compound of the count was that it exhibited "pharmacological effects on the central nervous system," which the applicants conceded was an inadequate disclosure. The applicants, however, relied upon a patent made of record as indicative of the general knowledge of one skilled in the art, which the applicants contended described a compound closely related to their claimed compound, to show utility or pharmacological activity for the compound of the count as an anticonvulsant. The court agreed with the board that there were sufficient structural dissimilarities between the compounds of the patent and those of the count to preclude reliance on the patent to

supplement the disclosure deficiencies of the foreign priority application.

In Knapp v. Anderson, 477 F.2d 588, 177 USPQ 688 (CCPA 1973), the court, citing to Blicke v. Treves, 241 F.2d 718, 112 USPQ 472 (CCPA 1957), stated that "[i]t is well settled that if the counts do not specify any particular use, evidence proving substantial utility for any purpose is sufficient to establish an actual reduction to practice." Id. at 590, 177 USPQ at 690 (emphasis added). Noting that the only utility contemplated for the compounds of the count was as ashless dispersants in lubricant compositions used in internal combustion engines, the court found no error in the Board's holding that there was no actual reduction to practice because only a potential utility had been established, this holding based upon the Board's finding of a lack of correlation between bench tests and actual service conditions in a combustion engine.

The CCPA has held that nebulous expressions, such as "biological activity" or "biological properties," disclosed in a specification convey little explicit indication regarding the utility of a compound. In re Kirk 376 F.2d 936, 941, 153 USPQ 48, 52 (CCPA 1967). But, while agreeing with the Board that the specification failed to disclose a specific allegation of utility for any compound within the scope of the claims, and that reference in the specification to biological properties of the claimed compound was so general and vague as to be meaningless, the court implied that a disclosure in the specification that the requisite properties of the claimed compounds are similar to those of a natural or synthetic hormone of known activity may, in appropriate circumstances, supplement an application to rectify an inadequate disclosure relating to the practical utility for the compound. Id. at 942, 153 USPQ at 53.

Every utility question arising in an interference, in the final analysis, must be decided on the basis of its own unique factual circumstances. Relevant evidence must be judged as a whole for its persuasiveness in determining whether the suggested use for the compound of the count is a practical utility. Cf. Nelson, 626 F.2d at 858, 206 USPQ at 885.

The Board has found that the Japanese priority application of Iizuka disclosed a practical utility for the compounds of the phantom count in the inhibition of thromboxane synthetase in human or bovine platelet microsomes, i.e., an in vitro utility. Clearly, this stated utility as found by the Board has been delimited with sufficient specificity to satisfy the threshold requirements of Kawai and Kirk. The stated utility of the Japanese priority application is directed to a specific pharmacological activity possessed by the imidazole derivatives of the phantom count -- the inhibition of thromboxane synthetase in vitro. Thus, this court on review is not presented with a general allegation of "biological activity" or "biological properties" as was the CCPA in Kirk, nor is reliance on prior art required to ascertain what specific pharmacological activity the compound of the count possesses, the factual situation confronting the court in Kawai.

The Japanese priority application, moreover, disclosed that it was generally known in the art, as of the critical date, that the parent imidazole and 1-methylimidazole compounds possessed an inhibitory action for thrombox

ane synthetase. Reliance on this disclosure in the specification of the pharmacological property of the parent imidazole and 1-methylimidazole compounds, as going towards proof of the pharmacological activity of the imidazole derivatives of the phantom count, is particularly relevant in the instant case, we believe, because Iizuka is not relying on this inference to supplement an inadequate disclosure in the Japanese priority application regarding the pharmacological activity of the compound of the phantom count, but rather is relying on this inference as cumulative probative evidence showing an adequately disclosed practical utility in the Japanese priority application.

This court, in Rey-Bellet and Kawai, has implied that a particular pharmacological activity identified with prior art compounds may have probative value as to the fact that the compound of the count possesses this particular pharmacological activity where there is a structural similarity between the prior art compounds and the compound of the count. Rey-Bellet, 493 F.2d at 1385-87, 181 USPQ at 456-58; Kawai, 480 F.2d at 890-91, 178 USPQ at 166-67. Cross has failed to proffer sufficient evidence or present any persuasive arguments going to the question of significant structural dissimilarities between the parent imidazole and 1-methylimidazole compounds and the imidazole derivatives of the phantom count. [17]

The expert of Iizuka, Dr. Ramwell, testified that, as of the critical date, there was an awareness on the part of those skilled in the art that the parent imidazole compound exhibited an inhibitory activity for thromboxane synthetase, in both in vitro and in vivo environments. Dr. Ramwell further testified that there was an awareness by those skilled in the art of a correlation between thromboxane A_2 and platelet aggregation, namely that thromboxane A_2 was a mediator in platelet aggregation. Several exhibits proferred by Iizuka corroborated Dr. Ramwell's testimony as to the general knowledge in the art with respect to the inhibitory effect of the parent imidazole compound for thromboxane synthetase. [18] Accordingly, the similar pharmacological activity of the parent imidazole and 1-methylimidazole compounds have probative value in the factual determination of practical utility for the compounds of the phantom count inasmuch as Cross has not met the burden of proof to establish structural dissimilarities between the parent imidazole and 1-methylimidazole compounds and the imidazole derivatives of the phantom count. Rey-Bellet, 493 F.2d at 1386-87, 181 USPQ at 457.

The Board found that there was adequate proof that the Japanese priority application disclosed a pharmacological activity for the compounds of the phantom count in inhibiting the action of thromboxane synthetase, similar to the pharmacological activity of the parent imidazole and 1-methylimidazole compounds which were found to possess an inhibitory action for thromboxane synthetase, this disclosed knowledge of the inhibitory

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action of the prior art compounds having been corroborated by testimony and documentary evidence. During the proceedings before the Board, the burden of proof rested upon Cross to show that the Japanese priority application was deficient. 37 C.F.R. §1.257(a). On review, Cross bears the burden of proof to show that the Board erred in finding that the Japanese priority application had adequately disclosed a practical utility. Reviewing the relevant evidence presented to the Board as a whole, we are not persuaded that Cross has met this burden of proof.

[1] The final question we must address is whether the inhibitory activity for thromboxane synthetase in human or bovine platelet microsomes, i.e., an in vitro utility, is sufficient to comply with the practical utility requirement of §101. Based upon the facts of this case, we are not persuaded that the Board erred in finding that the in vitro utility disclosed in the Japanese priority application for the compounds of the count is sufficient to establish a practical utility.

Our predecessor court has noted that adequate proof of any pharmacological activity constitutes a showing of practical utility. See, e.g., Nelson, 626 F.2d at 856, 206 USPQ at 883; Rey-Bellet, 493 F.2d at 1383, 181 USPQ at 454. Dr. Ramwell testified that initial testing of compounds for a particular pharmacological activity is typically done in vitro. In vitro testing permits an investigator to establish the rank order of compounds with respect to the particular pharmacological activity, i.e., to determine the relative potency of the compounds. Compounds having the highest ranking or potency are then selected for further testing in vivo. Presumably this is the accepted practice in the pharmaceutical industry inasmuch as Cross has not proferred any evidence refuting this testimony of Dr. Ramwell, and we note that this practice has an inherent logical persuasiveness. In vitro testing, in general, is relatively less complex, less time consuming, and less expensive than in vivo testing. Moreover, in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. Iizuka has not urged, and rightly so, that there is an invariable exact correlation between in vitro test results and in vivo test

results. Rather, Iizuka's position is that successful in vitro testing for a particular pharmacological activity establishes a significant probability that in vivo testing for this particular pharmacological activity will be successful.

As discussed above, Dr. Ramwell testified that the parent imidazole and 1-methylimidazole compounds had been subjected to both in vitro and in vivo testing as of the critical date, this corroborated by documentary evidence, and found to possess an inhibitory effect for thromboxane synthetase. Based upon this, Dr. Ramwell further testified that he would expect that in vivo testing of the imidazole derivatives of the phantom count would show that these compounds also possessed an inhibitory action for thromboxane synthetase, i.e., there would be a reasonable correlation between in vitro test results and in vivo test results. This evidence was found sufficient by the Board as proof that the Japanese priority application had disclosed a completed practical utility for the imidazole derivatives of the phantom count in inhibiting thromboxane synthetase in human or bovine platelet microsomes. Cf. Rey-Bellet, 493 F.2d at 1386-87, 181 USPQ at 457.

[2] Cross argues that the in vitro utility disclosed by the Japanese priority application is not per se useful, and that more sophisticated in vitro tests, using intact cells, or in vivo tests are necessary to establish a practical utility. [19] Cross is arguing that there must be a rigorous correlation of pharmacological activity between the disclosed in vitro utility and an in vivo utility to establish a practical utility. We, however, find ourselves in agrement with the Board that, based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. Cf. Nelson, 626 F.2d at 856, 206 USPQ at 883-83.

Our predecessor court has accepted evidence of in vivo utility as sufficient to establish a practical utility. See, e.g., Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881 (CCPA 1980); In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); Rey-Bellet v. Englehardt, 493 F.2d 1380, 181 USPQ 453 (CCPA 1974).

Opinions of our predecessor court have recognized the fact that pharmacological testing of animals is a screening procedure for testing new drugs for practical utility. See, e.g., In re Jolles, 628 F.2d 1322, 1327, 206 USPQ 885, 890 (CCPA 1980). This in vivo

testing is but an intermediate link in a screening chain which may eventually led to the use of the drug as a therapeutic agent in humans. We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question. Successful in vitro testing will marshal resources and direct the expenditure of effort to further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vivo utility. Cf. Nelson, 626 F.2d at 856, 206 USPQ at 883.

Today, under the circumstances of the instant case, where the Japanese priority application discloses an in vitro utility, i.e., the inhibition of thromboxane synthetase in human or bovine platelet microsomes, and where the disclosed in vitro utility is supplemented by the similar in vitro and in vivo pharmacological activity of structurally similar compounds, i.e., the parent imidazole and 1-methylimidazole compounds, we agree with the Board that this in vitro utility is sufficient to comply with the practical utility requirement of §101.

3. Enablement

The Board found that the knowledge as to the use of the pharmacological activity disclosed in the Japanese priority application lay in the fact that the system was a microsome system, microsome systems admittedly being known to those skilled in the art. Employing a microsome assay, the skilled worker could determine the relative strength of the compounds of the count vis-a-vis the known parent imidazole and 1-methylimidazole compounds. Thus, the dosage in the microsome assay milieu could be determined without inventive skill or undue experimentation.

Since we have agreed with the Board that the practical utility for the imidazole derivatives of the phantom count lies in their pharmacological activity in the microsome environment, the how-to-use requirement of §112 must be analyzed with reference to the microsome environment. We are confronted with a disclosure, similar to the situation before the court in Bundy, that fails to reveal dosages for the novel compounds per se. 642 F.2d at 434, 209 USPQ at 51. Although the Japanese priority application does disclose the fact that the imidazole derivatives of the phantom count possess a pharmacological activity similar to the parent imidazole and 1-methylimidazole compounds, the priority application, unlike the application in Bundy, does not disclose dosages for the parent imidazole and 1-methylimidazole compounds.

We agree with the Board, however, that this deficiency in the Japanese priority application is not fatal. The testimonial evidence of Dr. Ramwell, corroborated by certain documentary evidence, showed that those skilled in the art had available, at the critical date, information as to approximate dosage levels for the parent imidazole and 1-methylimidazole compounds to produce an I_{C50} effect, i.e., a 50% inhibition of thromboxane synthetase, in a microsome milieu. The objective of the pharmaceutical research undertaken by the parties was to discover imidazole derivatives having a potent inhibitory effect for thromboxane synthetase. Therefore, we believe it is logical, as did the Board, that the starting point for determining I_{C50} dosage levels for the imidazole derivatives of the phantom count would be the I_{C50} dosage levels of the parent imidazole and 1-methylimidazole compounds. The Board found that there was sufficient credible evidence that one skilled in the art, without the exercise of inventive skill or undue experimentation, could determine the I_{C50} dosage level for the imidazole derivatives of the phantom count in the microsome environment. Cf. Bundy, id., 209 USPQ at 51. We do not believe the Board erred in arriving at this conclusion. This is not a case such as In re Gardner, 427 F.2d 786, 166 USPQ 138 (1970), where the CCPA held that the applicant's disclosure was nonenabling because inventive skill and undue experimentation would be required to discover approprite dosages for humans, i.e., a therapeutic use. In the instant case, we are confronted with a pharmacological activity or practical utility, not a therapeutic use.

While we agree with the Board that the disclosure in the Japanese priority application is somewhat confusing with respect to the 2.5 x 10- 8level of molar concentrations, and that the 2-[p-(1-imidazolylmethyl) phenoxy]-acetic acid hydrochloride compound is outside the phantom count of the interference, this disclosed molar concentration, we believe, does provide some probative value going towards the sufficiency of the Japanese priority application for an enabling disclosure. The disclosed molar concentration would provide sufficient information as to an initial dosage level so that one skilled in the art could determine, without inventive skill or undue experimentation, the necessary molar concentrations for the imidazole derivatives of the phantom cOunt to achieve the desired pharmacological effect, i.e., the 50% inhibition of thromboxane synthetase in human or bovine platelet microsomes.

[3] The Board held the disclosure of the Japanese priority application adequate to satisfy the first paragraph of §112. The burden is on Cross to show Board error in arriving at this conclusion, and we are not persuaded that Cross has successfully carried this burden. Accordingly, we are satisfied that the how-to-use requirement of §112 has been complied with by the disclosures of the Japanese priority application.

Affirmed .

Footnotes

Footnote 1. We note a discrepancy, shown underlined in the above count, between the phantom count as set forth by the primary examiner and that reported by the Board in its decision. The phantom count set forth herein is the one propounded by the primary examiner. However, as will become apparent from the ensuing discussion, the substance of the phantom count is not crucial to resolution of the issues presented by this case.

Footnote 2. The formation of TXA 2in an arachidonic acid challenge is a sequential process initiated by the conversion of arachidonic acid to postaglandin PGG 2by the action of cyclooxygenase, which adds oxygen to the acid. Peroxidase converts the prostaglandin PGG 2to prostaglandin PGH 2, which in turn is converted by thromboxane synthetase to TXA 2.

Footnote 3. Iizuka's position is that, as of the "critical date" of his application, TXA 2was widely accepted in the art as causing platelet aggregation. Cross' position is that, as of the "critical date," platelet aggregation was believed to be nonspecific, i.e., platelet aggregation *may* occur in the presence of thromboxane synthetase, but thromboxane synthetase is not necessary for platelet aggregation. We note in retrospect that THE MERCK INDEX 1345-46 (10th ed. 1983) describes TXA 2as inducing irreversible platelet aggregation. More to the point, however, this court has noted that it is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests, nor is the inventor's theory or belief as to how his invention works a necessary element in the specification to satisfy the enablement requirement of 35 U.S.C. §112. Fromson v. Advance Offset Plate, Inc., 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983).

Footnote 4. Each party relies on the filing date of its foreign priority application to establish a constructive reduction to practice, the earliest date of invention to which each party is entitled under the patent laws of the United States. Kawai v. Metlesics, 480 F.2d 880, 885-86, 178 USPQ 158, 162 (CCPA 1973).

Footnote 5. More specifically, the issue before the Board was whether the Japanese priority application complied with the how-to-use requirement of 35 U.S.C. §112. Section 112 of Title 35 provides, in pertinent part, that:

> The specification shall contain a written description of the invention, of the manner and process of making and *using* it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and *use* the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention. (Emphasis added.)

Should Iizuka's Japanese priority application be found nonenabling with respect to the how-to-use requirement of §112, or otherwise found deficient under the patent laws of the United States, priority would be awarded to Cross based upon his unchallenged entitlement to the benefit of his British application.

Footnote 6. Generally, in vitro refers to an environment outside of a living organism, usually an artificial environment such as a test tube or culture. In contradistinction, in vivo generally refers to an environment within a living organism, such as a plant or animal, or it may refer to a particular portion of an organ external to the living organism, e.g., rat aortic loop.

Footnote 7. Utility is a fact question. Raytheon Co. v. Roper Corp., 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 127 (1984). Enablement under §112, paragraph 1, i.e., the how-to-use requirement, is a question of law. Id. at 960 n.6, 220 USPQ at 599 n.6.

Footnote 8. While questions one and two are closely connected, a thorough analysis of the utility issue requires first, a determination as to what utility is disclosed, i.e., the stated utility, for the invention claimed in the application. Only after the stated utility has been determined, can a proper analysis be undertaken to determine if the stated utility complies with the "practical utility" requirement of §101. As noted above, these questions regarding utility are factual in nature, see supra note 7, and are to be determined in the first instance by the PTO, the agency with the expertise in this regard.

Footnote 9. In applications prepared in the United States by experienced patent drafters, the drafter of the application typically sets forth objectives for the invention in the "Summary of the Invention" section of the application. These objectives will normally be consonant with the utility disclosed for the invention. As this court has noted, "[w]hen a properly claimed invention meets at least one stated objective, utility under §101 is clearly shown." Raytheon Co. v. Roper Corp., 724 F.2d 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 127 (1984).

Footnote 10. Under the facts of the instant case, utility and enablement questions are ancillary to priority. In the interference proceeding, Cross raised the issue as to whether the Japanese priority application contained sufficient disclosure to satisfy §112. As noted above, see supra note 5, if Cross prevails on this issue the Japanese priority application would be removed as the basis for awarding priority to Iizuka. See generally 37 C.F.R. §§1.225, .231, .258.

Footnote 11. A platelet microsome is an in vitro milieu consisting of blood platelets, the small, colorless corpuscles in the blood of all mammals, and other finely granular elements of protoplasm, such as ribosomes, fragmented endoplasmic reticula and mitochondrial christae.

Footnote 12. Generally, pharmacological activity refers to the properties and reactions of drugs, especially with relation to their therapeutic value.

Footnote 13. For purposes of the present opinion, we consider the phrase "substantial utility," as enunciated in Brenner, to be synonymous with the phrase "practical utility" as used in subsequent opinions of the CCPA.

Footnote 14. We recognize that Nelson dealt with tests which were found adequate to establish an actual reduction to practice, as opposed to a constructive reduction to practice. We agree with the Board that principles applicable to a determination of an actual reduction to practice are generally germane to a constructive reduction to practice.

Footnote 15. Both parties admitted that the GC-SMS test adequately simulated in vivo smooth muscle stimulation.

Footnote 16. The three tests, all in vivo type tests carried out on laboratory animals, were: (1) the Mental Health General Screening Test which indicated the physical response, or absence of a response, of test animals to a drug, indicating the presence, or absence, of a desired pharmacological activity; (2) the Tetrabenazine Antagonism Test which screened drugs for antidepressant activity; and (3) the Sidman Avoidance Test which screened drugs for tranquilizing activity.

Footnote 17. Contrary to Cross' contention in the Reply Brief, the evidence of record relied upon by Cross to show significant structural dissimilarity appears to us to be directed to the fact that there is a wide disparity in potency for thromboxane synthetase inhibition between the parent imidazole compound and prior art imidazole derivatives. Cross has not directed our attention to any specific evidence of record which establishes, or tends to establish, significant structural dissimilarities between the basic imidazole compound and the imidazole derivatives of the phantom count. Variation in potency, moreover, is a matter of degree of activity, see Bundy, 642 F.2d at 433, 209 USPQ at 51, but is still indicative of activity. There is no requirement that the compounds have the same degree of activity. Id., 209 USPQ at 51. Moreover, this argument may be construed as a tacit admission that the parent imidazole compound does possess the particular pharmacological activity of inhibiting thromboxane synthetase.

Along this line, we note that Dr. Smith, Cross' expert witness, testified generally, based upon the exhibits proffered by Iizuka, see infra note 18, that the parent imidazole compound possessed pharmacological activity for inhibiting thromboxane synthetase, although stating that there was a wide potency spectrum for prior art imidazole derivatives with respect to the parent imidazole compound.

Cross has directed the court's attention to the fact that the Japanese priority application, while disclosing that the parent imidazole and 1-methylimidazole compounds possess an inhibitory action for thromboxane synthetase, further discloses that this inhibitory effect is not satisfactory and that the parent imidazole and 1-methylimidazole compounds have not been put to practical therapeutic use. But a therapeutical utility is not necessarily synonymous to a pharmacological activity. Cf. Nelson, 626 F.2d at 856, 206 USPQ at 883.

Footnote 18. For example, Table I in the article "Imidazole: A Selective Inhibitor of Thromboxane Synthetase," PROSTAGLANDINS, Vol. 13, No. 4, April 1977 (Iizuka Exhibit No. 6), lists 1-methylimidazole and the parent imidazole compounds as possessing inhibitory activity for thromboxane synthetase, thereby offering corroboration of Dr. Ramwell's testimony.

The Board noted that Iizuka Exhibits 2-6 and 10-12, while inadmissible for the purpose of establishing the truth of what they say on their face, are admissible to bolster and support the testimony of Dr. Ramwell, as well as for the purpose of establishing what literature was available to the art at the critical time. Thus, for review purposes, we have examined these exhibits for their corroborating value with respect to Dr. Ramwell's testimony.

Footnote 19. Cross is seemingly arguing that the in vitro disclosure of the Japanese priority application is only a potential utility. See Knapp v. Anderson, 477 F.2d 588, 591, 177 USPQ 688, 691 (CCPA 1973).

- End of Case -

Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. (CA FC) 18 USPQ2d 1016

Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.

U.S. Court of Appeals Federal Circuit
18 USPQ2d 1016

Decided March 5, 1991
Nos. 90-1273, -1275

Headnotes

PATENTS

1. Patentability/Validity - Date of invention - Conception (§ 115.0403)

Conception of chemical compound requires that inventor be able to define compound so as to distinguish it from other materials, and to describe how to obtain it, rather than simply defining it solely by its principal biological property; thus, when inventor of ▶gene◀, which is chemical compound albeit complex one, is unable to envision detailed constitution of ▶gene◀ so as to distinguish it from other materials, as well as method for obtaining it, conception is not achieved until ▶reduction to practice◀ has occurred, and until after ▶gene◀ has been isolated.

2. Patentability/Validity - Date of invention - Conception (§ 115.0403)

Conception of generalized approach for screening DNA library that might be used to identify and clone erythropoietin ▶gene◀ of then-unknown constitution is not conception of "purified and isolated DNA sequence" encoding human EPA, since it is not "definite and permanent idea of the complete and operative invention."

3. Patentability/Validity - Obviousness - Relevant prior art - Particular inventions (§ 115.0903.03)

Federal district court did not err in holding non-obvious claims for purified and isolated DNA sequence encoding human hormone erythropoietin, in view of evidence showing that procedures may have been obvious to try, but also showing that there was no reasonable expectation of success.

4. Patentability/Validity - Specification - Best mode (§ 115.1107)

Determination of whether best mode requirement is satisfied is question of fact and thus is reviewed under clearly erroneous standard.

5. Patentability/Validity - Specification - Best mode (§ 115.1107)

Biological deposit is required to satisfy best mode requirement, for patents involving novel, genetically-engineered biological subject matter, if invention is incapable of being practiced without access to that organism, but if organism is created by insertion of genetic material into cell obtained from generally available sources, then cell deposit itself is not necessary and all that is required is description of best mode and adequate description of means of carrying out invention; if cells can be prepared without undue experimentation from known materials, based on description in patent specification, deposit is not required.

6. Patentability/Validity - Specification - Best mode (§ 115.1107)

Evidence showing that scientists were unable to duplicate inventor's genetically-heterogeneous best mode cell strain does not demonstrate that best mode requirement is not satisfied, since issue is whether disclosure is "adequate," and exact duplication is not necessary.

7. Patentability/Validity - Specification - Enablement (§ 115.1105)

Issue of whether claimed invention is enabled under 35 USC 112 is question of law that is reviewed de novo.

8. Patentability/Validity - Specification - Enablement (§ 115.1105)

Patent applicant is entitled to claim invention generically, if invention is described sufficiently to meet requirements of 35 USC 112; however, applicant, in claims for DNA sequences encoding erythropoietin, which has claimed every possible analog of ▸gene◂ containing about 4,000 nucleotides, but which has provided details for preparing only few EPO analog genes has not provided sufficient disclosure to support its claims, since, in view of structural complexity of EPO ▸gene◂, manifold possibilities for change in its structure, and uncertainty as to what utility will be possessed by these analogs, additional disclosure is needed as to identifying various analogs within scope of claim, methods for making them, and structural requirements for producing compounds with EPO-like activity.

9. Infringement - Defenses - Fraud or unclean hands (§ 120.1111)

Ultimate conclusion of inequitable conduct is reviewed under abuse of discretion standard, but underlying factual findings are reviewed under clearly erroneous standard.

10. Patentability/Validity - Specification - Enablement (§ 115.1105)

Federal district court erred by concluding that patent for method for purification of erythropoietin sufficiently enabled person of ordinary skill in art to obtain homogeneous EPO from natural sources having mean in vivo specific activity of at least 160,000, since court erred in accepting in vitro data as support for claims containing in vivo limitation.

11. Patentability/Validity - Specification - Claim adequacy (§ 115.1109)

Patent construction - Claims - Defining terms (§ 125.1305)

Claim whose meaning is in doubt is properly declared invalid, especially when there is close prior art; thus, federal district court did not err in holding that claim for homogeneous erythropoietin which has specific activity limitation of "at least about" 160,000 was indefinite, although such holding does not preclude any and all uses of term "about" in patent claims, since such term may be acceptable in appropriate fact situations.

Particular patents - Chemical - Erythropoietin

4,677,195, Hewick and Seehre, method for the purification of erythropoietin and erythropoietin compositions, claims 1, 3, 4, and 6 invalid.

4,703,008, Lin, DNA sequences encoding erythropoietin, claims 2, 4, and 6 valid and infringed; claims 7, 8, 23-27, and 29 invalid.

Case History and Disposition:

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Appeal from the U.S. District Court for the District of Massachusetts, Young, J. (Saris, U.S. magistrate); 13 USPQ2d 1737 .

Action by Amgen Inc. against Chugai Pharmaceutical Co. Ltd. and Genetics Institute Inc. for infringement of patent no. 4,703,008, to which defendants counterclaimed alleging infringement of patent no. 4,677,195. From federal district court decision holding certain claims of both patents valid and infringed, and holding other claims invalid, parties cross-appeal. Affirmed in part, reversed in part, and vacated in part.

Attorneys:
Edward M. O'Toole, Michael F. Borun, Richard A. Schnurr, and Christine A. Dudzik, of Marshall, O'Toole, Gerstein, Murray & Bicknell, Chicago, Ill.; Steven M. Odre and Robert D. Weist, Thousand Oaks, Calif., for Amgen.

Kurt E. Richter, Eugene Moroz, William S. Feiler, and Michael P. Dougherty, of Morgan & Finnegan, New York, N.Y., for Chugai Pharmaceutical.

William F. Lee, William McElwain, Ian Crawford, David Marder, David B. Bassett, and Sarianna T. Honkola, of Hale & Dorr, Boston, Mass., for Genetics Institute.

Judge:
Before Markey, Lourie, and Clevenger, circuit judges.

Opinion Text

Opinion By:

Lourie, J.

This appeal and cross appeal are from the March 4, 1990, judgment of the United States District Court for the District of Massachusetts, No. 87-2617-Y, *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 13 USPQ2d 1737 (1990), and involve issues of patent validity, infringement, and inequitable conduct with respect to two patents: U.S. Patent, 4,703,008 ('008), owned by Kirin-Amgen Inc. (Amgen), and U.S. Patent 4,677,195 ('195), owned by Genetics Institute, Inc. (GI).

Chugai Pharmaceutical Co., Ltd. (Chugai) and Genetics Institute, Inc. (collectively defendants) assert on appeal that the district court erred in holding that: 1) Amgen's '008 patent is not invalid under 35 U.S.C. §§102(g) and 103; 2) the '008 patent is enforceable; 3) the failure of Amgen to deposit the best mode host cells was not a violation of the best mode requirement under 35 U.S.C. §112; and 4) claims 4 and 6 of GI's '195 patent are invalid for indefiniteness under 35 U.S.C. §112.

On cross appeal, Amgen challenges the district court's holdings that: 1) claims 1 and 3 of the '195 patent are enabled; 2) the '195 patent is enforceable; 3) this is not an exceptional case warranting an award of attorney fees to Amgen; and 4) claims 7, 8, 23-27 and 29 of the '008 patent are not enabled by the specification.

We affirm the district court's holdings in all respects, except that we reverse the court's ruling that claims 1 and 3 of the '195 patent are enabled. We also vacate that part of the district court's judgment relating to infringement of those claims.

BACKGROUND 1

Erythropoietin (EPO) is a protein consisting of 165 amino acids which stimulates the production of red blood cells. It is therefore a useful therapeutic agent in the treatment of anemias or blood disorders characterized by low or defective bone marrow production of red blood cells.

The preparation of EPO products generally has been accomplished through the concentration and purification of urine from both healthy individuals and those exhibiting high EPO levels. A new technique for producing EPO is recombinant DNA technology in which EPO is produced from cell cultures into which genetically-engineered vectors containing the EPO gene have been introduced. The production of EPO by recombinant technology involves expressing an EPO gene through the same processes that occur in a natural cell.

THE PATENTS

On June 30, 1987, the United States Patent and Trademark Office (PTO) issued to Dr. Rodney Hewick U.S. Patent 4,677,195, entitled "Method for the Purification of Erythropoietin and Erythropoietin Compositions" (the '195 patent). The patent claims both homogeneous EPO and compositions thereof and a method for purifying human EPO using reverse phase high performance liquid chromatography. The method claims are not before us. The relevant claims of the '195 patent are:

1. Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement

as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least 160,000 IU per absorbance unit at 280 nanometers.

3. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogeneous erythropoietin of claim 1 in a pharmaceutically acceptable vehicle.

4. Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least about 160,000 IU per absorbance unit at 280 nanometers.

6. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogeneous erythropoietin of claim 4 in a pharmaceutically acceptable vehicle.

Dr. Hewick assigned the patent to GI.

The other patent in this litigation is U.S. Patent 4,703,008, entitled "DNA Sequences Encoding Erythropoietin" (the '008 patent), issued on October 27, 1987, to Dr. Fu-Kuen Lin, an employee of Amgen. The claims of the '008 patent cover purified and isolated DNA sequences encoding erythropoietin and host cells transformed or transfected with a DNA sequence. The relevant claims are as follows:

2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.

4. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 1, 2 or 3 in a manner allowing the host cell to express erythropoietin.

6. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 5.

7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.

8. A cDNA sequence according to claim 7.

23. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 7, 8, or 11 in a manner allowing the host cell to express said polypeptide.

24. A transformed or transfected host cell according to claim 23 which host cell is capable of glycosylating said polypeptide.

25. A transformed or transfected mammalian host cell according to claim 24.

26. A transformed or transfected COS cell according to claim 25.

27. A transformed or transfected CHO cell according to claim 25.

29. A procaryotic host cell stably transformed or transfected with a DNA vector according to claim 28.

PROCEDURAL HISTORY

On October 27, 1987, the same day that the '008 patent was issued, Amgen filed suit against Chugai and GI. It alleged that GI infringed the '008 patent by the production of recombinant EPO (rEPO) and by use of transformed mammalian host cells containing vectors with DNA coding for the production of human EPO, and that Chugai, as a result of a collaborative relationship with GI, had induced and/or contributed to the direct infringement of the '008 patent by GI. Amgen further sought a declaration that GI's '195 patent is invalid under 35 U.S.C. §§102, 103, and 112, or, in the alternative, that Amgen does not infringe the claims of the '195 patent, and a declaration that GI and Chugai's future activities in the production and sale of rEPO will infringe the '008 patent. 2

GI and Chugai answered and counterclaimed, asserting several affirmative defenses. including invalidity under 35 U.S.C. §§101, 102, 103, and 112; non-infringement; failure to make deposits at a public depository of biological materials allegedly necessary for enabling the best mode of practicing the invention; and unenforceability of the

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patent because of Amgen's alleged inequitable conduct before the PTO. GI also counterclaimed, alleging that Amgen infringed the '195 patent, asserting unfair competition, and seeking a declaratory judgment that the '008 patent was invalid and not infringed.

GI and Chugai then filed a joint motion for a partial summary judgment that Amgen infringed the claims of the '195 patent. Chugai also filed its own motion for summary judgment. On February 24, 1988, the district court granted GI's and Chugai's motion for partial summary judgment and, on January 31, 1989, the court granted Chugai's motion for partial summary judgment only to the extent of ruling that the '008 patent does not contain a process claim, an issue that is not now before us.

In response to Amgen's motion for a preliminary injunction, the district court, on February 7, 1989, issued an order finding that "Amgen had shown a reasonable likelihood of success on the merits of the validity of its patent; that it would suffer irreparable injury due to the needs of an incipient market and the attendant burdens on a new company; ..." and that, as to the public interest, "recombinant EPO is an extraordinarily valuable medicine that promises marked relief from renal failure." Because of this public interest finding, the court determined that it would not enter an order to delay or prevent production or shipping of EPO, but would require the defendant GI to place with the court all profits from the sale of EPO.

In order to expedite trial, the parties consented to trial before a magistrate. The judge entered judgment upon findings of fact and conclusions of law set forth by the magistrate. With respect to Amgen's '008 patent, the court held that claims 2, 4, and 6 are valid, enforceable and have been infringed by GI; that infringement was not willful; that claims 7, 8, 23-27, and 29 are invalid for lack of enablement under 35 U.S.C. §112 but, if valid, were infringed by GI; that the '008 patent does not contain a process claim; and that Chugai has not infringed, contributorily infringed, or induced infringement of any claim of the '008 patent. The court also dismissed Amgen's complaint against Chugai.

With respect to GI's '195 patent, the court concluded that claims 1 and 3 are valid, enforceable, and have been infringed by Amgen; that Amgen has not infringed claims 2 and 5; that Amgen's infringement was not willful; and that claims 4 and 6 are invalid for indefiniteness under 35 U.S.C. §112, but, if valid, were infringed by Amgen. The court also concluded that Amgen did not misuse the '008 patent and that this was not an "exceptional" case under 35 U.S.C. §285.

DISCUSSION

I. AMGEN's '008 PATENT (Lin)

A. *Alleged prior invention under 35 U.S.C. §102(g)*

The first issue we review is whether the district court erred in finding that the claims directed to a purified and isolated DNA sequence encoding human EPO were not invalidated by the work of GI's Dr. Fritsch. Section 102(g) provides in relevant part that:

A person is entitled to a patent unless-(g) before the applicant's invention thereof the invention was made ... by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Defendants assert error in the district court's legal conclusion that in this case Lin's conception occurred simultaneously with ▸reduction to practice◂. *See e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1376, 231 USPQ 81, 87 (Fed. Cir. 1988), *cert. denied,* 480 U.S. 947 (1987). They claim that Fritsch was first to conceive a probing strategy of using two sets of fully-degenerate cDNA probes of two different regions of the EPO ▸gene◂ to screen a gDNA library, which was the strategy which the district court found eventually resulted in the successful identification and isolation of the EPO ▸gene◂. Defendants further claim that Fritsch conceived this strategy in 1981, was diligent until he reduced the invention to practice in May of 1984, and thus should be held to be a 102(g) prior inventor over Lin, who reduced the invention to practice in September of 1983.

Conception is the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Hybritech,* 802 F.2d at 1376, 231 USPQ at 87 (citing 1 *Robinson on Patents* 532 (1890)); *Coleman v. Dines,* 754 F.2d 353, 359, 224 USPQ 857, 862 (Fed. Cir. 1985) (citing *Gunter v. Stream,* 573 F.2d 77, 80, 197 USPQ 482, 484 (CCPA 1978)). Conception requires both the idea of the inven

tion's structure and possession of an operative method of making it. *Oka v. Youssefyeh,* 849 F.2d 581, 583, 7 USPQ2d 1169, 1171 (Fed. Cir. 1988).

In some instances, an inventor is unable to establish a conception until he has reduced the invention to practice through a successful experiment. This situation results in a simultaneous conception and reduction to practice. *See* 3 D. Chisum, *Patents* §10.04[5] (1990). We agree with the district court that that is what occurred in this case.

The invention recited in claim 2 is a "purified and isolated DNA sequence" encoding human EPO. The structure of this DNA sequence was unknown until 1983, when the gene was cloned by Lin; Fritsch was unaware of it until 1984. As Dr. Sadler, an expert for GI, testified in his deposition: "You have to clone it first to get the sequence." In order to design a set of degenerate probes, one of which will hybridize with a particular gene, the amino acid sequence, or a portion thereof, of the protein of interest must be known. Prior to 1983, the amino acid sequence for EPO was uncertain, and in some positions the sequence envisioned was incorrect. Thus, until Fritsch had a complete mental conception of a purified and isolated DNA sequence encoding EPO and a method for its preparation, in which the precise identity of the sequence is envisioned, or in terms of other characteristics sufficient to distinguish it from other genes, all he had was an objective to make an invention which he could not then adequately describe or define.

[1] A ▸gene◂ is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. *See Oka,* 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.,* encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a ▸gene◂ so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until ▸reduction to practice◂ has occurred, *i.e.,* until after the ▸gene◂ has been isolated.

Fritsch had a goal of obtaining the isolated EPO gene, whatever its identity, and even had an idea of a possible method of obtaining it, but he did not conceive a purified and isolated DNA sequence encoding EPO and a viable method for obtaining it until after Lin. It is important to recognize that neither Fritsch nor Lin invented EPO or the EPO gene. The subject matter of claim 2 was the novel *purified and isolated* sequence which codes for EPO, and neither Fritsch nor Lin knew the structure or physical characteristics of it and had a viable method of obtaining that subject matter until it was actually obtained and characterized.

[2] Defendants further argue that because the trial court found that the probing and screening method employed by Lin is what distinguished the invention of the '008 patent over the prior art, Fritsch's strategy in 1981 had priority over Lin's use of that strategy. We disagree. The trial court found that Fritsch's alleged conception in 1981 of an approach that might result in cloning the gene was mere speculation. Conception of a generalized approach for screening a DNA library that might be used to identify and clone the EPO gene of then unknown constitution is not conception of a "purified and isolated DNA sequence" encoding human EPO. It is not "a definite and permanent idea of the complete and operative invention." Fritsch's conception of a process had to be sufficiently specific that one skilled in the relevant art would succeed in cloning the EPO gene. *See Coleman,* 754 F.2d at 359, 224 USPQ at 862. Clearly, he did not have that conception because he did not know the structure of EPO or the EPO gene.

The record indicates that several companies, as well as Amgen and GI, were unsuccessful using Fritsch's approach. As the trial court correctly summarized:

Given the utter lack of experience in probing genomic libraries with fully degenerate probes and the crudeness of the techniques available in 1981, it would have been mere speculation or at most a probable deduction from facts then known by Dr. Fritsch that his generalized approach would result in cloning the EPO gene.

13 USPQ2d at 1760. As expert testimony from both sides indicated, success in cloning the EPO ▸gene◂ was not assured until the ▸gene◂ was in fact isolated and its sequence known. Based on the uncertainties of the method and lack of information concerning the amino acid sequence of the EPO protein, the trial court was correct in concluding that neither party had an adequate conception of the DNA sequence until ▸reduction to practice◂

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had been achieved; Lin was first to accomplish that goal.

Defendants also argue that the court failed to consider that 1983, just prior to Lin's conception, was the relevant time for determining the completeness of Fritsch's conception, not 1981. However, the record shows that the court did consider what occurred in 1983. Moreover, Fritsch had no more of a conception in 1983 than he did in 1981, because he did not then know the sequence of the gene encoding EPO.

B. *Alleged obviousness of the inventions of claims 2, 4, and 6*

Claim 2, as noted above, recites a purified and isolated DNA sequence, and claims 4 and 6 are directed to host cells transformed with such a DNA sequence. The district court determined that claims 2, 4, and 6 are not invalid under 35 U.S.C. §103, concluding that the unique probing and screening method employed by Lin in isolating the EPO gene and the extensive effort required to employ that method made the invention nonobvious over the prior art. 3

Obviousness under Section 103 is a question of law. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568, 1 USPQ2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). The district court stated that one must inquire whether the prior art would have suggested to one of ordinary skill in the art that Lin's probing and screening method should be carried out and would have a reasonable expectation of success, viewed in light of the prior art. *See In re Dow Chemical Co.*, 837 F.2d 469 473, 5 uSPQ2d 1529, 1531 (Fed. Cir. 1988). "Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure." *Id.*

[3] The district court specifically found that, as of 1983, none of the prior art references "suggest[s] that the probing strategy of using two fully-redundant [sic] sets of probes, of relatively high degeneracy [sic], to screen a human genomic library would be likely to succeed in pulling out the gene of interest." 4 13 USPQ2d at 1768. While it found that defendants had shown that these procedures were "obvious to try," the references did not show that there was a reasonable expectation of success. *See In re O'Farrell*, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988).

Defendants challenge the district court's determination, arguing that, as of September 1983, one of ordinary skill in the art would have had a reasonable expectation of success in screening a gDNA library by Lin's method in order to obtain EPO. We agree with the district court's conclusion, which was supported by convincing testimony. One

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witness, Dr. Davies of Biogen, another biotechnology company that had worked on EPO, stated that he could not say whether Biogen scientists would have succeeded in isolating the EPO gene if Biogen had the EPO fragments that were available to Lin in 1983. Dr. Wall, a professor at UCLA, testified that it would have been "difficult" to find the gene in 1983, and that there would have been no more than a fifty percent chance of success. He said, "you couldn't be certain where in the genomic DNA your probe might fall." The court found that no one had successfully screened a genomic library using fully-degenerate probes of such high redundancy as the probes used by Lin. In the face of this and other evidence on both sides of the issue, it concluded that defendants had not shown by clear and convincing evidence that the procedures used by Lin would have been obvious in September 1983. We are not persuaded that the court erred in its decision.

Defendants assert that whether or not it would have been obvious to isolate the human EPO gene from a gDNA library with fully-degenerate probes is immaterial because it was obvious to use the already known monkey EPO gene as a probe. Defendants point out that, in the early 1980s, Biogen did significant work with an EPO cDNA obtained from a baboon, and that they used it as a probe to hybridize with the corresponding gene in a human gDNA library. However, this technique did not succeed until after Lin isolated the EPO gene with his fully-degenerate set of probes.

To support its obviousness assertion, defendants rely upon the testimony of their expert, Dr. Flavell, who testified that the overall homology of baboon DNA and human DNA was "roughly 90 percent". While this testimony indicates that it might have been feasible, perhaps obvious to try, to successfully probe a human gDNA library with a monkey cDNA probe, it does not indicate that the gene could have been identified and isolated with a reasonable likelihood of success. Neither the DNA nucleotide sequence of the human EPO gene nor its exact degree of homology with the monkey EPO gene was known at the time.

Indeed, the district court found that Lin was unsuccessful at probing a human gDNA library with monkey cDNA until after he had isolated the EPO gene by using the fully-degenerate probes. Based on the evidence in the record, the district court found there was no reasonable expectation of success in obtaining the EPO gene by the method that Lin eventually used. While the idea of using the monkey gene to probe for a homologous human gene may have been obvious to try, the realization of that idea would not have been obvious. There were many pitfalls. Hindsight is not a justifiable basis on which to find that ultimate achievement of a long sought and difficult scientific goal was obvious. The district court thoroughly examined the evidence and the testimony. We see no error in its result. Moreover, if the DNA sequence was not obvious, host cells containing such sequence, as claimed in claims 4 and 6, could not have been obvious. We conclude that the district court did not err in

holding that the claims of the patent are not invalid under Section 103.

C. *Best Mode*

Defendants argue that the district court erred in failing to hold the '008 patent invalid under 35 U.S.C. §112, asserting that Lin failed to disclose the best mammalian host cells known to him as of November 30, 1984, the date he filed his fourth patent application.

The district court found that the "best mode" of practicing the claimed invention was by use of a specific genetically-heterogeneous strain of Chinese hamster ovary (CHO) cells, which produced EPO at a rate greater than that of other cells. It further found that this strain was disclosed in Example 10 and that Lin knew of no better mode. GI argues that Lin's best mode was not adequately disclosed in Example 10 because one skilled in the art could not duplicate Lin's best mode without his having first deposited a sample of the specific cells in a public depository. The issue before us therefore is whether the district court erred in concluding that Example 10 of the '008 patent satisfied the best mode requirement as to the invention of the challenged claims 5 and that a deposit of the preferred CHO cells was not necessary.

[4] A determination whether the best mode requirement is satisfied is a question of fact, *DeGeorge v. Bernier,* 768 F.2d 1318, 1324, 226 USPQ 758, 763 (Fed. Cir. 1985); we

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therefore review the district court's finding under a clearly erroneous standard.

35 U.S.C. §112 provides in relevant part: The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, *and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

(Emphasis added).

This court has recently discussed the best mode requirement, pointing out that its analysis has two components. *Chemcast Corp. v. Arco Indus. Corp.,* 913 F.2d 923, 927, 16 USPQ2d 1033, 1036 (Fed. Cir. 1990). The first is a subjective one, asking whether, at the time the inventor filed his patent application, he contemplated a best mode of practicing his invention. If he did, the second inquiry is whether his disclosure is adequate to enable one skilled in the art to practice the best mode or, in other words, whether the best mode has been concealed from the public. The best mode requirement thus is intended to ensure that a patent applicant plays "fair and square" with the patent system. It is a requirement that the *quid pro quo* of the patent grant be satisfied. One must not receive the right to exclude others unless at the time of filing he has provided an adequate disclosure of the best mode known to him of carrying out his invention. Our case law has interpreted the best mode requirement to mean that there must be no concealment of a mode known by the inventor to be better than that which is disclosed. *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1384-85, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied,* 480 U.S. 947 (1987). Section 282 imposes on those attempting to prove invalidity the burden of proof. We agree that the district court did not err in finding that defendants have not met their burden of proving a best mode violation.

As noted above, the district court found that the best mode of making the CHO cells was set forth in Example 10. As the district court stated, while it was not clear which of two possible strains Lin considered to be the best, the cell strain subjected to 1000 nanomolar MTX (methotrexate) or that subjected to 100 nanomolar MTX, the best mode was disclosed because both were disclosed. 6 Defendants argue that this disclosure is not enough, that a deposit of the cells was required.

Defendants contend that "[i]n the field of living materials such as microorganisms and cell cultures," we should require a biological deposit so that the public has access to exactly the best mode contemplated by the inventor. This presents us with a question of first impression concerning the best mode requirement for patents involving novel genetically-engineered biological subject matter.

For many years, it has been customary for patent applicants to place microorganism samples in a public depository when such a sample is necessary to carry out a claimed invention. This practice arose out of the development of antibiotics, when microorganisms obtained from soil samples uniquely synthesized antibiotics which could not be readily prepared chemically or otherwise. *In re Argoudelis,* 434 F.2d 1390, 168 USPQ 99 (CCPA 1970). Such a deposit has been considered adequate to satisfy the *enablement* requirement of 35 U.S.C. §112, when a written description alone would not place the invention in the hands of the public and physical possession of a unique biological material is required. *See, e.g., In re Wands,* 858 F.2d 731, 735-36, 8 USPQ2d 1400, 1403 (Fed. Cir. 1988) ("Where an invention depends on the use of living materials ... it may be impossible to enable the public to make the invention (*i.e.,* to obtain these living materials) solely by means of written disclosure."); *In re Lundak,* 773 F.2d 1216, 1220, 227 USPQ 90, 93 (Fed. Cir. 1985) ("When an invention relates to a new biological material, the material may not be reproducible even when detailed procedures and a complete taxonomic description are included in the specification."); *see generally* Hampar, *Patenting of Recombinant DNA Technology: The Deposit Requirement,* 67 J. Pat. & Trademark Off. Soc'y 569, 607 (1985) ("The deposit requirement is a non-statutory mechanism for ensuring compliance with the 'enabling' provision under 35 U.S.C. §112.").

The district court found that the claims at issue require the use of biological materials

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that were capable of being prepared in the laboratory from readily available biological cells, using the description in Example 10. The court also found that there were no starting materials that were not publicly available, that were not described, or that required undue experimentation for their preparation in order to carry out the best mode. The court noted that Lin testified that the isolation of the preferred strain was a "routine limited dilution cloning procedure[ ]" well known in the art. Dr. Simonsen, GI's own expert, testified that the disclosed procedures were "standard" and that:

with the vectors and the sequences shown in Example 10, I have no doubt that someone eventually could reproduce-well, could generate cell lines [sic, strains] making some level of EPO, and they could be better, they could be worse in terms of EPO production.

The district court relied on this testimony, and, upon review, we agree with its determination. The testimony accurately reflects that the invention, as it relates to the *best mode* host cells, could be practiced by one skilled in the art following Example 10. Thus, the best mode was disclosed and it was adequately enabled.

[5] These materials are therefore not analogous to the biological cells obtained from unique soil samples. When a biological sample required for the practice of an invention is obtained from nature, the invention may be incapable of being practiced without access to that organism. Hence the deposit is required in that case. On the other hand, when, as is the case here, the organism is created by insertion of genetic material into a cell obtained from generally available sources, then all that is required is a description of the best mode and an adequate description of the means of carrying out the invention, not deposit of the cells. If the cells can be prepared without undue experimentation from known materials, based on the description in the patent specification, a deposit is not required. *See Feldman v. Aunstrup,* 517 F.2d 1351, 1354, 186 USPQ 108, 111 (CCPA 1975), ("No problem exists when the microorganisms used are known and readily available to the public."), *cert. denied,* 424 U.S. 912 [188 USPQ 720] (1976). Since the court found that that is the case here, we therefore hold that there is no failure to comply with the best mode requirement for lack of a deposit of the CHO cells, when the *best mode* of preparing the cells has been disclosed and the best mode cells have been enabled, *i.e.,* they can be prepared by one skilled in the art from known materials using the description in the specification.

Defendants also contend that the examiner's rejection of the application that matured into the '008 patent for failure to make a publicly accessible biological deposit supports its argument. U.S. Patent Application Serial No. 675,298, Prosecution History at 179 (First Rejection July 3, 1986). However, that rejection was withdrawn after an oral interview and a written argument that the invention did not require a deposit. *Id.* at 208.

We also note that the PTO has recently prescribed guidelines concerning the deposit of biological materials. *See* 37 C.F.R. §1.802(b) (1990) (biological material need not be deposited "if it is known and readily available to the public or can be made or isolated without undue experimentation"). The PTO, in response to a question as to whether the deposit requirement is applicable to the best mode requirement, as distinct from enablement, said:

The best mode requirement is a safeguard against the possible selfish desire on the part of some people to obtain patent protection without making a full disclosure. The requirement does not permit an inventor to disclose only what is known to be the second-best embodiment, retaining the best .... The fundamental issue that should be addressed is whether there was evidence to show the quality of an applicant's best mode disclosure is so poor as to effectively result in concealment. *In re Sherwood,* 615 F.2d 809, 204 USPQ 537 (CCPA 1980). If a deposit is the only way to comply with the best mode requirement then the deposit must be made.

52 *Fed.Reg.* 34080, 34086 (Sept. 8, 1987). 7

We see no inconsistency between the district court's decision, which we affirm here, and these guidelines.

[6] Defendants also assert that the record shows that scientists were unable to duplicate Lin's genetically-heterogeneous best mode cell strain. However, we have long held that the issue is whether the disclosure is "adequate," not that an exact duplication is necessary. Indeed, the district court stated that

he testimony is clear that no scientist could ever duplicate exactly the best mode used by Amgen, but that those of ordinary skill in the art could produce mammalian

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host cell strains or lines with similar levels of production identified in Example 10.

13 USPQ2d at 1774. What is required is an adequate disclosure of the best mode, not a guarantee that every aspect of the specification be precisely and universally reproducible. *See In re Gay,* 309 F.2d 769, 773, 135 USPQ 311, 316 (CCPA 1962).

Defendants finally argue that Lin's failure to deposit the transfected cells notwithstanding the fact that he was willing to deposit essentially worthless cell material was evidence of deliberate concealment. We have already stated that deposit of the host cells containing the rEPO gene was not necessary to satisfy the best mode requirement of Section 112. The best mode was disclosed and a deposit was not necessary to carry it out. Therefore, the fact that some cells were deposited, but not others, is irrelevant.

D. *Enablement of claims 7, 8, 23-27, and 29*

Amgen argues that the district court's holding that GI "provided clear and convincing evidence that the patent specification is insufficient to enable one of ordinary skill in the art to make and use the invention claimed in claim 7 of the '008 patent without undue experimentation" constituted legal error. 13 USPQ2d at 1776. Amgen specifically argues that the district court erred because it "did not properly address the factors which this court has held must be considered in determining lack of enablement based on assertion of undue experimentation," citing this court's decision in *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404.

Claim 7 is a generic claim, covering all possible DNA sequences that will encode any polypeptide having an amino acid sequence "sufficiently duplicative" of EPO to possess the property of increasing production of red blood cells. As claims 8, 23-27, and 29, dependent on claim 7, are not separately argued, and are of similar scope, they stand or fall with claim 7. *See In re Dillon,* 919 F.2d 688, 692, 16 USPQ2d 1897, 1900 (Fed. Cir. 1990) (in banc).

[7] Whether a claimed invention is enabled under 35 U.S.C. §112 is a question of law, which we review *de novo. Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1268, 229 USPQ 805, 811 (Fed. Cir. 1986), *cert. denied,* 479 U.S. 1030 (1987). "To be enabling under §112, a patent must contain a description that enables one skilled in the art to make and use the claimed invention." *Atlas Powder Co. v. E.I. duPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive. *Id.* The essential question here is whether the scope of enablement of claim 7 is as broad as the scope of the claim. *See generally In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970); 2 D. Chisum, *Patents* §7.03[7][b] (1990).

The specification of the '008 patent provides that:

one may readily design and manufacture genes coding for microbial expression of polypeptides having primary conformations which differ from that herein specified for mature EPO in terms of the identity or location of one or more residues (e.g., substitutions, terminal and intermediate additions and deletions).

DNA sequences provided by the present invention are thus seen to comprehend all DNA sequences suitable for use in securing expression in a procaryotic or eucaryotic host cell of a polypeptide product having at least a part of the primary structural conformation and one or more of the biological properties of erythropoietin, and selected from among: (a) the DNA sequences set out in FIGS. 5 and 6; (b) DNA sequences which hybridize to the DNA sequences defined in (a) or fragments thereof; and (c) DNA sequences which, but for the degeneracy of the genetic code, would hybridize to the DNA sequences defined in (a) and (b).

The district court found that over 3,600 different EPO analogs can be made by substituting at only a single amino acid position, and over a million different analogs can be made by substituting three amino acids. The patent indicates that it embraces means for preparation of "numerous" polypeptide analogs of EPO. Thus, the number of claimed DNA encoding sequences that can produce an EPO-like product is potentially enormous.

In a deposition, Dr. Elliott, who was head of Amgen's EPO analog program, testified that he did not know whether the fifty to eighty EPO analogs Amgen had made "had the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake." Based on this evidence, the trial court concluded that "defendants had provided clear and convincing evidence that the patent specification is insufficient to enable one of ordinary skill in the art to make and use the invention claimed in claim 7 of the '008 patent without undue experimentation." 13 USPQ at 1776. In making this determina

tion, the court relied in particular on the lack of predictability in the art, as demonstrated by the testimony of both Dr. Goldwasser, another scientist who worked on procedures for purifying urinary EPO (uEPO), and Dr. Elliott. After five years of experimentation, the court noted, "Amgen is still unable to specify which analogs have the biological properties set forth in claim 7." *Id.*

We believe the trial court arrived at the correct decision, although for the wrong reason. By focusing on the biological properties of the EPO analogs, it failed to consider the enablement of the DNA sequence analogs, which are the subject of claim 7. Moreover, it is not necessary that a patent applicant test all the embodiments of his invention, *In re Angstadt,* 537 F.2d 498, 502, 190 USPQ 214, 218 (CCPA 1976); what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims. For DNA sequences, that means disclosing how to make and use enough sequences to justify grant of the claims sought. Amgen has not done that here. In addition, it is not necessary that a court review all the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory. What is relevant depends on the facts, and the facts here are that Amgen has not enabled preparation of DNA sequences sufficient to support its all-encompassing claims.

[8] It is well established that a patent applicant is entitled to claim his invention generically, when he describes it sufficiently to meet the requirements of Section 112. *See Utter v. Hiraga,* 845 F.2d 993, 998, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. §112¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses."); *In re Robins,* 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) ("[R]epresentative samples are not required by the statute and are not an end in themselves."). Here, however, despite extensive statements in the specification concerning all the analogs of the EPO gene that can be made, there is little enabling disclosure of particular analogs and how to make them. Details for preparing only a few EPO analog genes are disclosed. Amgen argues that this is sufficient to support its claims; we disagree. This "disclosure" might well justify a generic claim encompassing these and similar analogs, but it represents inadequate support for Amgen's desire to claim all EPO gene analogs. There may be many other genetic sequences that code for EPO-Type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them.

In affirming the district court's invalidation of claims 7, 8, 23-27, and 29 under Section 112, we do not intend to imply that generic claims to genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by an applicant. That is not the case here, where Amgen has claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make EPO and a very few analogs.

The district court properly relied upon *Fisher* 8 in making its decision. In that case, an applicant was attempting to claim an adrenocorticotrophic hormone preparation containing a polypeptide having at least twenty-four amino acids of a specified sequence. Only a thirty-nine amino acid product was disclosed. The court found that applicant could not obtain claims that are insufficiently supported and hence not in compliance with the first paragraph of 35 U.S.C. §112. It stated:

Appellant's parent application, therefore, discloses no products, inherently or expressly, containing other than 39 amino acids, yet the claim includes all polypeptides, of the recited potency and purity, having at least 24 amino acids in the chain in the recited sequence. The parent specification does not enable one skilled in the art to make or obtain ACTHs with other than 39 amino acids in the chain, and there has been no showing that one of ordinary skill would have known how to make or obtain such other ACTHs without undue experimentation. As for appellant's conclusion that the 25th to 39th acids in the chain are unnecessary, it is one thing to make such a statement when persons skilled in the art are able to make or obtain ACTH having other than 39 amino acids; it is quite another thing when they are not able to do so. In the latter situation, the statement is in no way "enabling" and hence lends no further support for the broad claim. We conclude that appellant's parent applica

tion is insufficient to support a claim as broad as claim 4.

requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Fisher, 427 F.2d at 836, 839, 166 USPQ at 21-2224.

Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, with attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity. Under the circumstances, we find no error in the court's conclusion that the generic DNA sequence claims are invalid under Section 112.

E. *Inequitable Conduct*

Defendants argue that the '008 patent claims are unenforceable as a result of an asserted misrepresentation of the number of probes Lin used for the monkey gene cloning described in Example 3 of his patent. Relying on the district court's finding that Lin had said that a "full set" mixture of 128 "EpV" probes 9 was used for monkey cDNA screening, whereas only a 16-member "subset" of the EpV mixture was actually used, defendants argue that the court ought to have found that the representations were material.

[9] The essential elements of proof of inequitable conduct include intent to deceive and materiality. After finding threshold levels of materiality and intent, the trial court must balance the two and determine, in its discretion, whether inequitable conduct has occurred. *J.P. Stevens & Co. v. Lex Tex Ltd., Inc.,* 747 F.2d 1553, 1560, 223 USPQ 1089, 1092 (Fed. Cir. 1984), *cert. denied,* 474 U.S. 822 (1985). While we review an ultimate conclusion of inequitable conduct under an abuse of discretion standard, *Kingsdown Medical Consultants, Ltd. v. Hollister Inc.,* 863 F.2d 867, 876, 9 USPQ2d 1384, 1392 (Fed. Cir. 1988) (in banc), *cert. denied,* 490 U.S. 1067 (1989), the underlying factual threshold findings are reviewed under a clearly erroneous standard.

Lin set out to clone the EPO gene by more than one method, including using degenerate human probes and monkey probes. It is not disputed that he did isolate the human EPO gene from a genomic library using two different 128-member pools of probes made from fragments of the human EPO protein. Thereafter, he also attempted to use the human sequence probes to find the monkey EPO cDNA to be used later as a probe to hybridize with the human EPO gene. Example 3 of the '008 patent describes this work, indicating that the screening yielded seven positive clones. It also reports that a subset of the human EpV mixture was used for DNA sequencing work. When Lin published his monkey cDNA cloning work in a scientific journal, he also reported the use of 128 EpV probes to screen the monkey library. Lin screened the monkey library with the full mixture of 128 EpV probes and with one of eight subsets of probes which made up the full EpV mixture. In response to a question whether a subset of EpV probes was used in the first screening of the monkey cDNA library, Lin testified:

I don't know which we used, the subset first or used the full set first. I cannot recall exactly. It looks like the subset was first defining the number, yes.

This answer constituted the sole basis for the court's finding that, "[a]t trial, Lin admitted he only used a subset of the EpV 128 probes in screening the cDNA library." 13 USPQ2d at 1778.

We consider that the district court's finding of an "admission" of misrepresentation in Lin's testimony and its conclusion that GI "presented clear and convincing evidence of a misrepresentation" was clearly erroneous. That Lin did not recall whether he first screened the monkey cDNA library with a full set of probes or a subset of probes, and his answer that "it looks like" he used the subset, are certainly not clear admissions that he only used a subset. However, the district court was correct in concluding that, even if there had been an erroneous statement, it was not material because Lin succeeded in cloning the EPO gene first with his use of the fully-degenerate probes. Thus, his testimony does not provide clear and convincing evidence that he misrepresented to the PTO the number of probes used. He did use 128-member probes as well as a subset. Moreover, this evidence does not create an inference of an intent to mislead. The court

properly concluded that there was no inequitable conduct in prosecuting the '008 patent.

II. GI's '195 PATENT (Hewick)

A. *Enablement of claims 1 and 3*

Amgen challenges the district court's determination that "the '195 patent enables a person of ordinary skill in the art to obtain homogeneous EPO [including rEPO and uEPO] from natural sources" having a mean *in vivo* specific activity of at least 160,000. 10 13 USPQ2d at 1794. Claims 1 and 3 contain the limitation that EPO have a specific activity of at least 160,000 IU/AU. The district court found, based upon expert testimony from both sides, that to those skilled in the art, in the absence of an express statement in the patent, the claims would be construed to refer to *in vivo* rather than *in vitro* specific activity. To support its challenge, Amgen asserts that the district court's determination is contradicted by GI's own bioassay data and by the district court's finding that "the '195 patent fails to enable the purification of rEPO." Amgen also asserts that the district court erred in relying solely on an *in vitro* measure of specific activity, having initially construed the '195 claims as requiring an *in vivo* measure to avoid invalidity for indefiniteness.

35 U.S.C. §112 requires that an invention be described "in such full, clear, concise, and exact terms as to enable any person skilled in the art ... to make and use the same." We review a determination of enablement as a question of law. *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1268, 229 USPQ 805, 811 (Fed. Cir. 1986), *cert. denied*, 479 U.S. 1030 (1987).

We do not consider the court's finding that the assay measurement was an *in vivo* one to be erroneous in view of the testimony it heard. That being the case, the question is whether the court erred in concluding that the claims requiring 160,000 IU/AU by an *in vivo* measurement were enabled. We conclude that it did err.

Defendants have produced no evidence that it ever prepared EPO with a specific activity of at least 160,000 IU/AU *in vivo* using the disclosed methods. In its report to the FDA, GI stated that it had purified uEPO material "to homogeneity" by subjecting partially purified uEPO material to reverse phase high performance liquid chromatography (RP-HPLC), the technique taught by Hewick in the '195 patent. The district court found that GI reported to the FDA that the specific activity of uEPO, based on *in vivo* bioassays, was only 109,000 IU/AU. 11 GI originally arrived at the figure of 160,000 IU/AU by calculation, before it had the capacity to derive quantitative information from bioassays. Hewick subjected the EPO to RP-HPLC, the EPO having an actual value of 83,000 IU/AU. After weighing the chromatograph, he found that "at least fifty percent" of the area under the chromatograph curve was attributable to something other than EPO. He then doubled the 83,000, and arrived at a theoretical specific activity of "at least about 160,000 IU/AU." That procedure, while possibly valid as a means for estimating the specific activity of a pure sample, does not establish that GI had a workable method for actually obtaining the pure material that it claimed.

Moreover, the work of others shows that Hewick did not enable the preparation of uEPO having an *in vivo* specific activity of at least 160,000, as the claims required. Dr. Kawakita, a scientist at Kummamoto University in Japan, reported an *in vivo* specific activity of 101,000 IU/AU when using RP-HPLC according to Hewick's method. This is similar to the 109,000 value reported to the FDA by GI. Kawakita did report a value of 188,000, but did not follow the teachings in the '195 patent. Defendants also rely on the testimony of Fritsch that "I've also seen further data in Chugai's PLA indicating additional urinary EPO preparation that had activities of 190,000, I believe, units per absorbance unit." However, the document to which Fritsch referred was not offered into evidence by GI after Amgen objected to its introduction and is not before us.

Defendants argue that Dr. Kung's uEPO test result of 173,640 IU/AU in an *in vitro* test supports the enablement of its claims. Amgen argues that an *in vivo* test result would only have been 65 percent of the *in vitro* result and thus would not have met the 160,000 IU/AU limitation of the claims. The district court relied on Kung, despite the demonstrated disparity between the results of *in vitro* and *in vivo* testing.

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[10] It is not absolutely clear to us that, for uEPO, the *in vivo* specific activity is 65 percent of the *in vitro* specific activity. Nonetheless, Kung's measurement, being *in vitro,* does not demonstrate enablement of the claimed invention, and that fact means that the court erred in finding enablement. Added to this fact is the difference that exists between the *in vivo* results for rEPO and uEPO 12 , and the other lack of support for the 160,000 limitation. Under these circumstances, we hold that the district court erred in accepting the *in vitro* data as support for claims containing what has been found to be an *in vivo* limitation.

In addition to the question of enablement regarding uEPO, the district court found that the only purification attempt on rEPO in the manner set out in the '195 patent failed to provide homogeneous EPO. The patent itself, in Example 2, discloses GI's purification efforts on rEPO and indicates that GI did not obtain purified rEPO. As the district court found, "[t]he patent does not contain any procedures ... for purifying rEPO to the point that RP-HPLC will be successful." 13 USPQ2d at 1758. Thus, the patent fails to enable purification of either rEPO or uEPO. 13 *See In re Rainer,* 377 F.2d 1006, 1012, 153 USPQ 802, 807 (CCPA 1967) ("specification is evidence of its own inadequacy").

The burden of showing non-enablement is Amgen's, not GI's, but in the case of a challenged patent, when substantial discovery has occurred, and there is no credible evidence that the claimed purified material can be made by those skilled in the art by the disclosed process, and all evidence from both the inventor and his assignee and from third parties is to the contrary, we conclude that Amgen has met its burden to show that the claims have not been adequately enabled. We do not hold that one must always prove that a disclosed process operates effectively to produce a claimed product. But, under these circumstances, we conclude that the court erred in holding that claims 1 and 3 were properly enabled.

B. *Indefiniteness of claims 4 and 6*

The district court held claims 4 and 6 of the '195 patent invalid because their specific activity limitation of "at least about 160,000" was indefinite. Defendants challenge this holding, asserting that there is no evidence that claims 4 and 6 do not comply with the requirements of 35 U.S.C. §112.

The statute requires that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." A decision as to whether a claim is invalid under this provision requires a determination whether those skilled in the art would understand what is claimed. *See Shatterproof Glass Corp. v. Libbey-Owens Ford Co.,* 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985) (Claims must "reasonably apprise those skilled in the art" as to their scope and be "as precise as the subject matter permits."). The district court found that "bioassays provide an imprecise form of measurement with a range of error" and that use of the term "about" 160,000 IU/AU, coupled with the range of error already inherent in the specific activity limitation, served neither to distinguish the invention over the close prior art (which described preparations of 120,000 IU/AU), nor to permit one to know what specific activity values below 160,000, if any, might constitute infringement. 13 USPQ2d at 1787. It found evidence of ambiguity in the fact that Chugai, GI's partner, itself questioned whether the specific activity value of 138,000 IU/AU for its own rEPO was within the claim coverage.

In prosecuting the '195 patent, GI disclosed to the examiner a publication by Miyake et al., which discloses a uEPO product having an *in vivo* specific activity of 128,620 IU/AU. When the examiner noticed this disclosure late in the prosecution, he rejected the '195 claims with a specific activity limitation of "at least 120,000" as anticipated by the Miyake et al. disclosure. It was only after the "at least 120,000" claims were cancelled that GI submitted the "at least about 160,000" claim language.

The court found the "addition of the word 'about' seems to constitute an effort to recapture ... a mean activity somewhere between 120,000, which the patent examiner found was anticipated by the prior art, and [the] 160,000 IU/AU" claims which were previously allowed. Because "the term 'about' 160,000 gives no hint as to which mean value between the Miyake et al. value of 128,620 and the mean specific activity level of 160,000 constitutes infringement," the court held the "at least about" claims to be invalid for indefiniteness. 13 USPQ2d at 1787-88. This holding was further supported by the fact that nothing in the specification, prosecution history, or prior art provides any

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indication as to what range of specific activity is covered by the term "about," and by the fact that no expert testified as to a definite meaning for the term in the context of the prior art. In his testimony, Fritsch tried to define "about" 160,000, but he could only say that while "somewhere between 155 [,000] might fit within that number," he had not "given a lot of direct considerations to that...."

[11] When the meaning of claims is in doubt, especially when, as is the case here, there is close prior art, they are properly declared invalid. *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 453, 227 USPQ 293, 297 (Fed. Cir. 1985). We therefore affirm the district court's determination on this issue. We also note that, in view of our reversal of the district court's holding that claims 1 and 3 are valid, it is clear that claims 4 and 6 would also be invalid without the "about" limitation. In arriving at this conclusion, we caution that our holding that the term "about" renders indefinite claims 4 and 6 should not be understood as ruling out any and all uses of this term in patent claims. It may be acceptable in appropriate fact situations, *e.g., W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983) ("use of 'stretching ... at a rate exceeding about 10% per second' in the claims is not indefinite"), even though it is not here.

C. *Inequitable Conduct*

The district court concluded that GI did not engage in inequitable conduct with respect to the '195 patent. Amgen challenges this holding, asserting, *inter alia,* that GI displayed an intent to mislead by withholding data showing *in vivo* specific activity of homogenous uEPO and withholding information on the range of error in EPO bioassays.

It is fundamental that to establish inequitable conduct, an intent to deceive is required. *RCA Corp. v. Data General Corp.*, 887 F.2d 1056, 1065, 12 USPQ2d 1449, 1456-57 (Fed. Cir. 1989). A finding of an intent to deceive may follow from an assessment of materiality, knowledge, and surrounding circumstances, including evidence of good faith. *Kingsdown Medical Consultants Ltd. v. Hollister Inc.*, 863 F.2d 867, 876, 9 USPQ2d 1384, 1392 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1067 (1989). The district court found no such intent, stating:

the record is devoid of any evidence that would establish deliberate knowing withholdings of any kind by Dr. Hewick or GI. Dr. Hewick was a credible witness who spoke carefully and candidly about his work ... There is no evidence that Dr. Hewick withheld any information he believed was material to the patent examiner.

Amgen, 13 USPQ2d at 1791. There is no clear error in this finding. Amgen raises no inequitable conduct issues that were not fully considered by the district court. We have reviewed the record and find no abuse of discretion on the part of the district court. This is also not an exceptional case.

III. OTHER ISSUES

In view of our conclusion that the district court erred as a matter of law in holding that claims 1 and 3 of the '195 patent are not invalid, we vacate the district court's holdings relating to infringement of those claims. We have considered the other arguments by counsel on both sides and find them to be without merit.

CONCLUSION

We conclude that the district court did not err in its findings that claims 2, 4, and 6 of the '008 patent are valid and enforceable and have been infringed by GI, and that claims 7, 8, 23-27, and 29 of the '008 patent are invalid; we therefore affirm the judgment of the court regarding the '008 patent. Because we conclude that claims 1, 3, 4, and 6 of the '195 patent are invalid, we affirm the judgment concerning claims 4 and 6 and reverse the judgment concerning claims 1 and 3.

COSTS

Each party shall bear its own costs.

AFFIRMED-IN-PART, REVERSED-IN-PART, VACATED-IN-PART

Footnotes

Footnote 1. The district court, in a detailed opinion, fully sets out the scientific and historical background relating to the patents at issue. *See Amgen,* 13 USPQ2d at 1741-58. Familiarity with that opinion is presumed.

Footnote 2. Amgen subsequently filed a complaint with the United States International Trade Commission alleging that Chugai's importation of rEPO, manufactured in Japan using genetically engineered host cells, violated Section 337 of the Tariff Act of 1930 (19 U.S.C. §§1337, 1337a). The Commission entered an order terminating the investigation for lack of subject matter jurisdiction. This court vacated and remanded, holding that the Commission should have treated the complaint on the merits and not on jurisdictional grounds, and that the claims of Amgen's patent did not cover a process for producing rEPO. *Amgen, Inc. v. United States Int'l Trade Comm'n,* 902 F.2d 1532, 14 USPQ2d 1734 (Fed. Cir. 1990).

Footnote 3. We note that both the district court and the parties have focused on the obviousness of a process for making the EPO gene, despite the fact that it is products (genes and host cells) that are claimed in the patent, not processes. We have directed our attention accordingly, and do not consider independently whether the products would have been obvious aside from the alleged obviousness of a method of making them.

Footnote 4. At this point, some explanation of the involved technology may be useful, consistent with that expressed in the district court opinion. DNA consists of two complementary strands of nucleotides, which include the four basic compounds adenine(A), guanine(G), cytosine(C), and thymine(T), oriented so that bases from one strand weakly bond to the bases of the opposite strand. A bonds with T, and G bonds with C to form complementary base pairs. This bonding process is called hybridization and results in the formation of a stable duplex molecule. The structure also includes 5-carbon sugar moieties with phosphate groups.

The genetic code for a particular protein depends upon sequential groupings of three nucleotides, called codons. Each codon codes for a particular amino acid. Since there are four nucleotide bases and three bases per codon, there are 64 (4x4x4) possible codons. Because there are only 20 natural amino acids, most amino acids are specified by more than one codon. This is referred to as a "redundancy" or "degeneracy" in the genetic code, a fact that complicates and renders more difficult the techniques of recombinant DNA.

In order to prepare a protein using recombinant DNA technology, the gene for the protein must first be isolated from a cell's total DNA by screening a library of that cell's DNA. The DNA library is screened by use of a probe, a synthetic radiolabelled nucleic acid sequence which can be used to detect and isolate complementary base sequences by hybridization. To design a probe when the gene has not yet been isolated, a scientist must know the amino acid sequence, or a portion thereof, of the protein of interest. Because some amino acids have several possible codons and the researcher cannot know which of the possible codons will actually code for an amino acid, he or she may decide to design a set of probes that covers all possible codons for each amino acid comprising the protein, known as a "fully-degenerate" set of probes. A library to be screened can be a genomic library (gDNA), which contains a set of all the DNA sequences found in an organism's cells or a complementary DNA (cDNA) library, which is much smaller and less complex than a gDNA library, and is used frequently when the tissue source for a given gene is known.

Footnote 5. Defendants assert that all the claims should be invalid for failure to disclose the best mode. We perceive that the best mode issue only relates to the host cell claims, 4, 6, 23-27, and 29. Absent inequitable conduct, a best mode defense only affects those claims covering subject matter the practice of which has not been disclosed in compliance with the best mode requirement. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 940, 15 USPQ2d 1321, 1328 (Fed. Cir.), *cert. denied*, — U.S. —, 111 S.Ct. 296 (1990).

Footnote 6. In its opinion, the district court stated that "the best way to express EPO was from mammalian cells ... and that a cell line derived from 11 possible clones from the CHO B11, 3,.1 cell strain was to be used for Amgen's master working cell bank, which was expected to be started on November 26, 1984." 13 USPQ2d at 1772. At another point, the court stated that Amgen "did disclose the best mode in Example 10 of the invention, when it described the production rates of the 100 nanomolar-amplified cells (the B11 3,.1 cell strain) and one micromolar-treated cells." *Id.*

Footnote 7. *See also* 53 *Fed. Reg.* 39420, 39425 (Oct. 6, 1989) (comment *re* "deposit [to] satisfy the best mode requirement"); 52 *Fed. Reg.* 34080, 34080 and 34084 (Sept. 8, 1987) (deposit may be required to satisfy enablement, best mode, or distinct claim requirements of §112).

Footnote 8. *Cf. Hormone Research Foundation, Inc. v. Genentech, Inc.*, 904 F.2d 1558, 15 USPQ2d 1039 (Fed. Cir. 1990). In *Hormone Research,* this court, in a remand, directed the district court to consider the effect of *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 8 USPQ2d 1461 (Fed. Cir. 1989) and *In re Hogan,* 559 F.2d 595, 194 USPQ 527 (CCPA 1977) on *Fisher* in its enablement analysis. The facts of our case are distinguishable from those in *Hormone Research, United States Steel,* and *Hogan.*

Footnote 9. The probes designated "EpV" were from EPO amino acid sequence region 46-52.

Footnote 10. The potency of EPO in the '195 patent is stated as its specific activity, expressed as a ratio of International Units (which measures the ability of EPO to cause formation of red blood cells) per absorbance unit (the amount of light absorbed by a sample of EPO measured by a spectrophotometer at a given wavelength, 280 nanometers), *i.e.*, IU/AU.

Footnote 11. Defendants provided no evidence that faulty purification procedures or other missteps caused its failure to obtain 160,000 IU/AU *in vivo* material as claimed in the '195 patent.

Footnote 12. The court quoted Chugai to the effect that the *in vivo* activity of uEPO is 65 percent that of rEPO.

Footnote 13. Chugai's sample reported to the Food and Drug Administration was not purified by the disclosed process.

- End of Case -

In re BUTING, 163 USPQ 689 (CCPA 1969)

In re BUTING

(CCPA)
163 USPQ 689

Decided Dec. 4, 1969
No. 8210
U.S. Court of Customs and Patent Appeals

Headnotes

PATENTS

1. Patentability—Utility (§ 51.75)

Amount of evidence of utility required depends on facts of each case; character and amount of evidence needed may vary, depending on whether alleged operation described appears to accord with or to contravene established scientific principles and beliefs; while tests demonstrating effectiveness of compounds in treating diseases in animals are not to be disregarded, such tests must be viewed with respect to utility asserted; where application is specifically directed toward treatment of humans, clinical case histories showing that compound is useful in treating two types of cancer do not establish utility of compound for treatment of other kinds of cancer in humans; such evidence, limited to one compound and two types of cancer, is not commensurate with broad scope of utility asserted and claimed, viz., that of treating seven types of cancer with several compounds; it is incumbent upon applicant to limit claims to area where utility has not been properly challenged or to submit evidence refuting the challenge.—In re Buting (CCPA) 163 USPQ 689.

Particular patents—Cancer Treatment

Buting, Composition and Methods for Treating Malignant Diseases, claims 6 to 8 of application refused.—In re Buting (CCPA) 163 USPQ 689.

Case History and Disposition:

Appeal from Board of Appeals of the Patent Office.

Application for patent of Walter E. Buting, Serial No. 346,401, filed Feb. 21, 1964; Patent Office Group 120. From decision rejecting claims 6 to 8, applicant appeals. Affirmed.

Attorneys:
EVERETT F. SMITH, Indianapolis, Ind. (LEROY WHITAKER, Houston, Tex., of counsel) for appellant.

JOSEPH SCHIMMEL (LEROY B. RANDALL and JACK E. ARMORE of counsel) for Commissioner of Patents.

Judge:

Before RICH, Acting Chief Judge, MATTHEWS, Judge, sitting by designation, and ALMOND, BALDWIN, and LANE, Associate Judges.

Opinion Text

Opinion By:
ALMOND, Judge.

This is an appeal from the decision of the Patent Office Board of Appeals affirming the rejection of claims 6, 7 and 8 of appellant's application. [1] No claims have been allowed.

The invention before us relates to a method of treating a malignant condition, i.e. cancer, in humans by the administration of one of a group of compounds known as bis (b-aziridino-ethyl) sulfones. It is stated that significant activity of the compounds has been demonstrated against a broad spectrum of experimental neoplasms including certain leukemias, sarcomas, adenocarcinomas, and lymphosarcomas, when the drugs are given by a variety of routes including intraperitoneal, subcutaneous and oral administration.

Confirmation of the activity by clinical treatment of human subjects is alleged. As proof of the asserted utility, appellant presented, in the specification and by affidavit, evidence of efficacy against a spectrum of leukemia and ascitic and solid tumors in experimental mice of two of the claimed sulfones as well as results of the treatment of two human patients, one with Hodgkin's disease and the other with chronic myelogenous leukemia, with a composition comprising bis [b-(2-methylaziridino) ethyl] sulfone in 95 percent aqueous ethanol. In the patient suffering from Hodgkin's disease, reduction in the nodes in the inguinal and axillary regions of more than 75 percent and a marked decrease in pulmonary infiltrates were observed during treatment. The patient suffering from chronic myelogenous leukemia experienced a remission of the lesions during treatment with the composition.

Claim 6 is representative:

> 6. The method of treating a malignant condition selected from the group consisting of leukemias, sarcomas,
>
> Page 690
>
> adenocarcinomas, lymphosarcomas, melanomas, myelomas, and ascitic tumors which comprises the administration to a patient suffering from said disease of a therapeutically effective amount of a compound of the formula
> *Graphic material consisting of a chemical formula or diagram set at this point is not available. See text in hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.*
> wherein R 1and R 2are selected from the group consisting of hydrogen, methyl, and ethyl.

Claims 7 and 8 are drawn to methods employing species embraced within the genus of claim 6.

The sole question involved in the appeal is whether the demonstrated evidence of efficacy, summarized above, is sufficient, under 35 U.S.C. 101, to support an allegation of utility in humans.

The examiner thought not, finding it unapparent that one skilled in the art would accept the clinical data as statistically significant evidence that all the compounds are safe and effective in humans against all the malignant diseases specified in the claims, citing In re Krimmel, 48 CCPA 1116, 292 F.2d 948, 130 USPQ 215 ; In re Novak, 49 CCPA 1283, 306 F.2d 924, 134 USPQ 335 ; In re Citron, 51 CCPA 852, 325 F.2d 248, 139 USPQ 516 .

In affirming, the board stated that insofar as the claims were directed to a method of treating humans for conditions heretofore regarded as incurable or, at best, subject to remission, clear and convincing evidence of utility for the claimed purpose would be required. The board then concluded:

> We are not aware of any reputable authority which would accept appellant's two clinical cases as establishing utility for treatment of cancer in humans. As was pointed out in Brenner v. Manson, 148 USPQ 689, a process to be patentable must produce a useful result and be of substantial utility not merely of scientific interest or for further testing. In this case further testing seems necessary.

Appellant attacks the board's decision by arguing that existing law does not require large numbers of clinical cases for proof of utility. The cases relied on by the Patent Office are alleged to be either irrelevant to the present fact situation or to fail to support the position expounded by the examiner and board. Acknowledging that, in appropriate circumstances, proof of utility may be required by the Patent Office, appellant contends, nevertheless, that the Patent Office has erred in the nature and quantum of the proof called for, in that no case law supports the proposition that *extensive* clinical data are necessary to support an allegation of utility directed to human therapy. The test, it is urged, is as stated in the concurring opinion in In re Hartop, 50 CCPA 780, 311 F.2d 249, 135 USPQ 419, "whether 'the invention has been brought to such perfection as to be capable of practical employment'."

The record, appellant argues, contains detailed evidence of the efficacy of the drug from which those skilled in the art would conclude that utility in humans has been demonstrated. The board ignored, it is alleged, the evidence with respect to animals and failed to appreciate the remarkable success obtained with the two human patients, one of whom had been unsuccessfully treated with two established anticancer agents. The qualifications of appellant's expert who concluded that the drug used was a safe, effective and useful agent in the area of cancer chemotherapy were not challenged. That the drug may not be ready for marketing for human therapy, appellant points out, does not detract from its patentability.

[1] We agree with appellant that the prior decisions relied on by the Patent Office are of little assistance in the situation before us. In In re Irons, 52 CCPA 938, 340 F.2d 974, 144 USPQ 351, this court said that the proofs of utility should be convincing to one skilled in the art; however, it is evident that the *amount* of evidence required depends on the facts of each individual case. In re Gazave, 54 CCPA 1524, 379 F.2d 973, 154 USPQ 92. The character and amount of evidence needed may vary, depending on whether the alleged operation described appears to accord with or to contravene established scientific principles and beliefs. In re Chilowsky, 43 CCPA 775, 229 F.2d 457, 108 USPQ 321.

Nor do we find Brenner v. Manson, 383 U.S. 519, 148 USPQ 689, apposite. There the question was whether the *alleged utility* was sufficient to satisfy the requirement of 35 U.S.C. 101, and not whether any such alleged utility had been *proved.* The issue before us concerns degree of proof, not the statutory sufficiency of the utility asserted.

The solicitor contends that the test to be applied is the acceptability to those skilled in the art both of the asserted utility and of the evidence submitted to prove the assertion, if evidence is necessary. He requests that this court

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judicially notice medical publications, appended to his brief, alleged to show that those skilled in the art conclude that it is not possible to extrapolate data obtained in one particular species with a particular tumor to another species. Thus, having removed the animal test data as supporting proof for the utility alleged, there are left only two case histories of one compound to prove utility for seven separate classes of tumors for the entire class of compounds defined in the claims on appeal. Such evidence, it is argued, is insufficient.

We need not consider the materials presented by the solicitor, for this court observed in Krimmel, supra, at 1123, 130 USPQ at 219:

> We wish to point out that this court is aware of the common practice of using "experimental animals" in considerable variety for the evaluation of chemical compounds for possible pharmaceutical applications prior to clinical testing on humans. It is also our understanding that a demonstration that a compound has desirable or beneficial properties in the prevention, alleviation, or cure of some disease or manifestation of a disease in experimental animals does not necessarily mean that the compound will have the same properties when used with humans.

While the court's consideration of tests demonstrating effectiveness of compounds in treating diseases in animals indicates that such are not to be disregarded, it is clear that such tests must be viewed with respect to the utility asserted. [2] Here, appellant acknowledges that "the application on appeal is specifically directed toward the treatment of human subjects" and the utility asserted is essentially that expressed in the opening phrase of claim 6, reproduced previously. Appellant has shown by clinical case histories only that bis [b-(2-methylaziridino) ethyl] sulfone is useful in treating Hodgkin's disease and chronic myelogenous leukemia. While the Patent Office tribunals appear to have accepted this observation and evidence, they challenge its adequacy as establishing utility for the stated purposes of treatment of the other kinds of cancer in humans recited in the claims.

We do not find such evidence, limited to one compound and two types of cancer, to be commensurate with the broad scope of utility asserted and claimed, viz. that of treating seven types of cancer with several compounds. Rather, we think it incumbent upon an appellant either to limit his claims to the area where utility has not been properly challenged or to submit evidence refuting that challenge. In re Harwood, 55 CCPA 922, 390 F.2d 985, 156 USPQ 673 .

Since appellant has done neither, the decision of the board is, accordingly, *affirmed.*

Footnotes

Footnote 1. Serial No. 346,401, filed February 21, 1964, for "Composition and Methods for Treating Malignant Diseases."

Footnote 2. See In re Krimmel, supra, In re Bergel, 48 CCPA 1102, 292 F.2d 955, 130 USPQ 206 , and In re Hitchings, 52 CCPA 1141, 342 F.2d 80, 144 USPQ 637 .

- End of Case -

All Other Cases
In re Brana (CA FC) 34 USPQ2d 1436 (3/30/1995)

In re Brana (CA FC) 34 USPQ2d 1436

In re Brana

U.S. Court of Appeals Federal Circuit
34 USPQ2d 1436

Decided March 30, 1995
No. 93-1393

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Headnotes

PATENTS

1. Patentability/Validity -- Utility (§ 115.10)

Patentability/Validity -- Specification -- Enablement (§ 115.1105)

Application for pharmaceutical invention did not fail to disclose specific disease against which claimed compounds are useful, and thereby fail to satisfy enablement requirement of 35 USC 112, since specification, which favorably compares compounds of invention with known compounds found to be highly effective against lymphocytic leukemia tumor models, implicitly asserts that claimed compounds are also highly effective against those models, and since tumor models are cell lines representing specific lymphocytic tumors.

2. Patentability/Validity -- Utility (§ 115.10)

Patentability/Validity -- Specification -- Enablement (§ 115.1105)

Patent and Trademark Office improperly rejected, for lack of utility, application claims for pharmaceutical compounds used in cancer treatment in humans, since neither nature of invention nor evidence proferred by PTO would cause one of ordinary skill in art to reasonably doubt asserted utility, and since even if utility of compounds could be reasonably questioned, evidence that compounds within scope of claims, and other structurally similar compounds, are effective as chemotherapeutic agents in animals would be sufficient to convince one skilled in art of asserted utility; absence of evidence that claimed compounds have chemotherapeutic effect in humans does not warrant contrary conclusion, since proof of alleged pharmaceutical property for compound by statistically significant tests using standard experimental animals is sufficient to establish utility.

Case History and Disposition:

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Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Patent application of Miguel F. Brana, Jose M.C. Berlanga, Marina M. Moset, Erich Schlick and Gerhard Keilhauer, serial no. 07/533,944, filed June 4, 1990, which is a continuation of serial no. 213,690, filed June 30, 1988. From decision upholding examiner's rejection of claims 10-13, applicants appeal. Reversed.

Attorneys:
Malcolm J. MacDonald, Herbert B. Keil, and David S. Nagy, Washington, D.C., for appellants.

Fred E. McKelvey, Solicitor, PTO; Albin F. Drost, Deputy Solicitor; Richard E. Schafer, Teddy S. Gron, Joseph G. Piccolo and Richard L. Torczon, Associate Solicitors, for appellee.

Judge:
Before Plager, Lourie, and Rader, circuit judges.

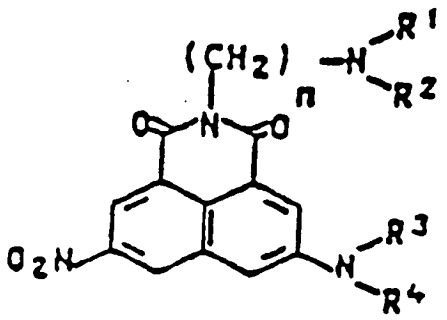
Opinion Text

Opinion By:
Plager, J.

Miguel F. Brana, *et al.* (applicants), appeal the March 19, 1993 decision of the United States Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), in Appeal No. 92-1196. The Board affirmed the examiner's rejection of claims 10-13 of patent application Serial No. 533,944 under 35 U.S.C. Section 112 Para.1 (1988). 1 The examiner's rejection, upon which the Board relied in rendering its decision, was based specifically on a challenge to the utility of the claimed compounds and the amount of experimentation necessary to use the compounds. We conclude the Board erred, and reverse.

I. BACKGROUND

On June 30, 1988, applicants filed patent application Serial No. 213,690 (the '690 application) 2 directed to 5-nitrobenzo [de]isoquinoline-1,3-dione compounds, for use as antitumor substances, having the following formula:



where n is 1 or 2, R [1] and R [2] are identical or different and are each hydrogen,

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C1-C6-alkyl, C1-C6-hydroxyalkyl, pyrrolidinyl, morpholino, piperidinyl or piperacinyl, and R [3] and R [4] are identical or different and are each hydrogen, C1-C6-alkyl, C1-C6-acyl, C2-C7-alkoxycarbonyl, ureyl, aminocarbonyl or C2-C7-alkylaminocarbonyl. These claimed compounds differ from several prior art benzo [de]isoquinoline-1,3-dione compounds due to the presence of a nitro group (O2N) at the 5-position and an amino or other amino group (NR [3]R [4]) at the 8-position of the isoquinoline ring.

The specification states that these non- symmetrical substitutions at the 5- and 8-positions produce compounds with "a better action and a better action spectrum as antitumor substances" than known benzo [de]isoquinolines, namely those in K.D. Paull et al., *Computer Assisted Structure- Activity Correlations, Drug Research, 34(II),* 1243-46 (1984) (Paull). Paull describes a computer-assisted evaluation of benzo [de]isoquinoline-1,3-diones and related compounds which have been screened for antitumor activity by testing their efficacy *in vivo* 3 against two specific implanted murine (i.e., utilizing mice as test subjects) lymphocytic leukemias, P388 and L1210. 4 These two *in vivo* tests are widely used by the National Cancer Institute (NCI) to measure the antitumor properties of a compound. Paull noted that one compound in particular, benzo [de]isoquinoline-1,3(2H)dione,5-amino-2(2-dimethyl-aminoethyl [sic]) (hereinafter "NSC 308847"), was found to show excellent activity against these two specific tumor models. Based on their analysis, compound NSC 308847 was selected for further studies by NCI. In addition to comparing the effectiveness of the claimed compounds with structurally similar compounds in Paull, applicants' patent specification illustrates the cytotoxicity of the claimed compounds against human tumor cells, *in vitro,* 5 and concludes that these tests "had a good action." 6

The examiner initially rejected applicants' claims in the '690 application as obvious under 35 U.S.C. Section 103 in light of U.S. Patent No. 4,614,820, issued to and referred to hereafter as Zee-Cheng *et al.* Zee-Cheng *et al.* discloses a benzo [de]isoquinoline compound for use as an antitumor agent with symmetrical substitutions on the 5-position and 8-position of the quinoline ring; in both positions the substitution was either an amino or nitro group. 7 Although not identical to the applicants' claimed compounds, the examiner noted the similar substitution pattern (i.e., at the same positions on the isoquinoline ring) and concluded that a mixed substitution of the invention therefore would have been obvious in view of Zee-Cheng *et al.*

In a response dated July 14, 1989, the applicants rebutted the Section 103 rejection. Applicants asserted that their mixed disubstituted compounds had unexpectedly better antitumor properties than the symmetrically substituted compounds in Zee-Cheng *et al.* In support of this assertion applicants attached the declaration of Dr. Gerhard Keilhauer. In his declaration Dr. Keilhauer reported that his tests indicated that applicants' claimed compounds were far more effective as antitumor agents than the compounds disclosed in Zee-Cheng *et al.* when tested, *in vitro,* against two specific types of human tumor cells, HEp and HCT-29. 8 Applicants further noted that, although the differences between the compounds in Zee-Cheng *et al.* and applicants' claimed compounds were slight, there was no suggestion in the art that these improved results (over Zee-Cheng *et al.*) would have been

expected. Although the applicants overcame the Section 103 rejection, the examiner nevertheless issued a final rejection, on different grounds, on September 5, 1989.

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On June 4, 1990, applicants filed a continuation application, Serial No. 533,944 (the '944 application), from the above-mentioned '690 application. Claims 10-13, the only claims remaining in the continuation application, were rejected in a final office action dated May 1, 1991. Applicants appealed the examiner's final rejection to the Board.

In his answer to the applicants' appeal brief, the examiner stated that the final rejection was based on 35 U.S.C. Section 112 Para.1. 9 The examiner first noted that the specification failed to describe any specific disease against which the claimed compounds were active. Furthermore, the examiner concluded that the prior art tests performed in Paull and the tests disclosed in the specification were not sufficient to establish a reasonable expectation that the claimed compounds had a practical utility (i.e. antitumor activity in humans). 10

In a decision dated March 19, 1993, the Board affirmed the examiner's final rejection. The three-page opinion, which lacked any additional analysis, relied entirely on the examiner's reasoning. Although noting that it also would have been proper for the examiner to reject the claims under 35 U.S.C. Section 101, the Board affirmed solely on the basis of the Examiner's Section 112 Para.1 rejection. This appeal followed.

II. DISCUSSION

At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant prove regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago. 11 We note the Commissioner has recently addressed this question in his Examiner Guidelines for Biotech Applications, *see* 60 Fed. Reg. 97 (1995); 49 Pat. Trademark & Copyright J. (BNA) No. 1210, at 234 (Jan. 5, 1995).

The requirement that an invention have utility is found in 35 U.S.C. Section 101: "Whoever invents . . . any new and *useful* . . . composition of matter . . . may obtain a patent therefor. . . ." (emphasis added). It is also implicit in Section 112 Para.1, which reads:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it.

As noted, although the examiner and the Board both mentioned Section 101, and the rejection appears to be based on the issue of whether the compounds had a practical utility, a Section 101 issue, the rejection according to the Board stands on the requirements of Section 112 Para.1. It is to that provision that we address ourselves. 12 The Board gives two reasons for the rejection; 13 we will consider these in turn.

1.

The first basis for the Board's decision was that the applicants' specification failed to disclose a specific disease against which the

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claimed compounds are useful, and therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.* , 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied,* 480 U.S. 947 (1987). In support, the Commissioner argues that the disclosed uses in the '944 application, namely the "treatment of diseases" and "antitumor substances," are similar to the nebulous disclosure found insufficient in *In re Kirk,* 376 F.2d 936, 153 USPQ 48 (CCPA 1967). This argument is not without merit.

In *Kirk* applicants claimed a new class of steroid compounds. One of the alleged utilities disclosed in the specification was that these compounds possessed "high biological activity." *Id.* at 938, 153 USPQ at 50. The specification, however, failed to disclose which biological properties made the compounds useful. Moreover, the court found that known specific uses of similar compounds did not cure this defect since there was no disclosure in the specification that the properties of the claimed compounds were the same as those of the known similar compounds. *Id.* at 942, 153 USPQ at 53. Furthermore, it was not alleged that one of skill in the art would have known of any specific uses, and therefore, the court concluded this alleged use was too obscure to enable one of skill in the art to use the claimed invention. *See also Kawai v. Metlesics,* 480 F.2d 880, 178 USPQ 158 (CCPA 1973).

[1] *Kirk* would potentially be dispositive of this case were the above-mentioned language the only assertion of utility found in the '944 application. Applicants' specification, however, also states that the claimed compounds have "a better action and a better action spectrum as antitumor substances" than known compounds, specifically those analyzed in Paull. As previously noted, *see supra* note 4, Paull grouped various benzo [de]isoquinoline-1,3-diones, which had previously been tested *in vivo* for antitumor activity against two lymphocytic leukemia tumor models (P388 and L1210), into various structural classifications and analyzed the test results of the groups (i.e. what percent of the compounds in the particular group showed success against the tumor models). Since one of the tested compounds, NSC 308847, was found to be highly effective against these two lymphocytic leukemia tumor models, 14 applicants' favorable comparison implicitly asserts that their claimed compounds are highly effective (i.e. useful) against lymphocytic leukemia. An alleged use against this particular type of cancer is much more specific than the vaguely intimated uses rejected by the courts in *Kirk* and *Kawai. See, e.g., Cross v. Iizuka,* 753 F.2d at 1048, 224 USPQ at 745 (finding the disclosed practical utility for the claimed compounds -- the inhibition of thromboxane synthetase in human or bovine platelet microsomes -- sufficiently specific to satisfy the threshold requirement in *Kirk* and *Kawai.*)

The Commissioner contends, however, that P388 and L1210 are not diseases since the only way an animal can get sick from P388 is by a direct injection of the cell line. The Commissioner therefore concludes that applicants' reference to Paull in their specification does not provide a specific disease against which the claimed compounds can be used. We disagree.

As applicants point out, the P388 and L1210 cell lines, though technically labeled tumor models, were originally derived from lymphocytic leukemias in mice. Therefore, the P388 and L1210 cell lines do represent actual specific lymphocytic tumors; these models will produce this particular disease once implanted in mice. If applicants were required to wait until an animal naturally developed this specific tumor before testing the effectiveness of a compound against the tumor *in vivo,* as would be implied from the Commissioner's argument, there would be no effective way to test compounds *in vivo* on a large scale.

We conclude that these tumor models represent a specific disease against which the claimed compounds are alleged to be effective. Accordingly, in light of the explicit reference to Paull, applicants' specification alleges a sufficiently specific use.

2.

The second basis for the Board's rejection was that, even if the specification did allege a specific use, applicants failed to prove that the claimed compounds are useful. Citing various references, 15 the Board found, and the Commissioner now argues, that the tests offered by the applicants to prove utility

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were inadequate to convince one of ordinary skill in the art that the claimed compounds are useful as antitumor agents. 16

This court's predecessor has stated:

[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of Section 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. *Id.* at 224, 169 USPQ at 370. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *See In re Bundy,* 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981). 17

[2] The PTO has not met this initial burden. The references cited by the Board, Pazdur and Martin, 18 do not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of *in vivo* murine tests -- relevant only if applicants must prove the ultimate value in humans of their asserted utility. Likewise, we do not find that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness.

The purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. *In re Jolles,* 628 F.2d at 1327, 206 USPQ at 890. Modern science has previously identified numerous successful chemotherapeutic agents. In addition, the prior art, specifically Zee Cheng *et al.* , discloses structurally similar compounds to those claimed by the applicants which have been proven *in vivo* to be effective as chemotherapeutic agents against various tumor models.

Taking these facts -- the nature of the invention and the PTO's proffered evidence -- into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO thus has not satisfied its initial burden. Accordingly, applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. *See In re Marzocchi,* 439 F.2d at 224, 169 USPQ at 370.

We do not rest our decision there, however. Even if one skilled in the art would have reasonably questioned the asserted utility, i.e., even if the PTO met its initial burden thereby shifting the burden to the applicants to offer rebuttal evidence, applicants proffered sufficient evidence to convince one of skill in the art of the asserted utility. In particular, applicants provided through Dr. Kluge's declaration 19 test results showing that several compounds within the scope of the claims exhibited significant antitumor activity against the L1210 standard tumor

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model *in vivo*. Such evidence alone should have been sufficient to satisfy applicants' burden.

The prior art further supports the conclusion that one skilled in the art would be convinced of the applicants' asserted utility. As previously mentioned, prior art -- Zee Cheng *et al.* and Paull -- disclosed structurally similar compounds which were proven *in vivo* against various tumor models to be effective as chemotherapeutic agents. Although it is true that minor changes in chemical compounds can radically alter their effects on the human body, *Kawai,* 480 F.2d at 891, 178 USPQ at 167, evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility. *See Rey-Bellet v. Engelhardt,* 493 F.2d 1380, 181 USPQ 453 (CCPA 1974); *Kawai,* 480 F.2d 880, 178 USPQ 158 .

The Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means *in vivo* testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans. 20 The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. *See Scott v. Finney,* 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.").

Our court's predecessor has determined that proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility. *In re Krimmel,* 292 F.2d 948, 953, 130 USPQ 215, 219 (CCPA 1961); *see also In re Bergel,* 292 F.2d 958, 130 USPQ 205 (CCPA 1961). In concluding that similar *in vivo* tests were adequate proof of utility the court in *In re Krimmel* stated:

We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.

Krimmel, 292 F.2d at 953, 130 USPQ at 219. Moreover, NCI apparently believes these tests are statistically significant because it has explicitly recognized both the P388 and L1210 murine tumor models as standard screening tests for determining whether new compounds may be useful as antitumor agents.

In the context of this case the Martin and Pazdur references, on which the Commissioner relies, do not convince us otherwise. Pazdur only questions the reliability of the screening tests against lung cancer; it says nothing regarding other types of tumors. Although the Martin reference does note that some laboratory oncologists are skeptical about the predictive value of *in vivo* murine tumor models for human therapy, Martin recognizes that these tumor models continue to contribute to an increasing human cure rate. In fact, the authors conclude that this perception (i.e. lack of predictive reliability) is not tenable in light of present information.

On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical studies. *See* 21 U.S.C. Section 355(i)(1); 5 C.F.R. Section 312.23 (a)(5), (a)(8) (1994). Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimes. *See* 21 C.F.R. Section 312.21(b).

FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott,* 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the

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associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

In view of all the foregoing, we conclude that applicants' disclosure complies with the requirements of 35 U.S.C. Section 112 Para.1.

3.

The Commissioner takes this opportunity to raise the question of this court's standard of review when deciding cases on appeal from the PTO. Traditionally we have recited our standard of review to be, with regard to questions of law, that review is without deference to the views of the Agency, *In re Donald son,* 16 F.3d 1189, 1192, 29 USPQ2d 1845, 1848 (Fed. Cir. 1994) (in banc), *In re Caveney,* 761 F.2d 671, 674, 226 USPQ 1, 3 (Fed. Cir. 1985), and with regard to questions of fact, we defer to the Agency unless its findings are "clearly erroneous." *See, e.g., In re Baxter Travenol Labs,* 952 F.2d 388, 21 USPQ2d 1281 (Fed. Cir. 1991); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990); *In re De Blauwe,* 736 F.2d 699, 222 USPQ 191 (Fed. Cir. 1984).

With regard to judgment calls, those questions that fall " [s]omewhere near the middle of the fact-law spectrum," this court has recognized "the falseness of the fact-law dichotomy, since the determination at issue, involving as it does the application of a general legal standard to particular facts, is probably most realistically described as neither of fact nor law, but mixed." *Campbell v. Merit Systems Protection Board,* 27 F.3d 1560, 1565 (Fed. Cir. 1994). When these questions of judgment are before us, whether we defer, and the extent to which we defer, turns on the nature of the case and the nature of the judgment. *Id.* ("Characterization therefore must follow from an *a priori* decision as to whether deferring . . . is sound judicial policy. We would be less than candid to suggest otherwise.").

The Commissioner contends that the appropriate standard of review for this court regarding questions of law, of fact, and mixed questions of law and fact, coming to us from the PTO is found in the Administrative Procedure Act (APA) at 5 U.S.C. Section 706. The standard set out there is that " [t]he reviewing court shall . . . hold unlawful and set aside agency action, findings, and conclusions found to be -- (A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law; . . . (E) unsupported by substantial evidence. . . ." The Commissioner is of the view that the stated standard we now use, which is the traditional standard of review for matters coming from a trial court, is not appropriate for decisions coming from an agency with presumed expertise in the subject area, and is not in accord with law. 21

Applicants argue that by custom and tradition, recognized by the law of this court, the standard of review we have applied, even though inconsistent with the standard set forth in the APA, nevertheless is a permissible standard. In our consideration of this issue, there is a reality check: would it matter to the outcome in a given case which formulation of the standard a court articulates in arriving at its decision? The answer no doubt must be that, even though in some cases it might not matter, in others it would, otherwise the lengthy debates about the meaning of these formulations and the circumstances in which they apply would be unnecessary.

A preliminary question, then, is whether this is one of those cases in which a difference in the standard of review would make a difference in the outcome. The ultimate issue is whether the Board correctly applied the Section 112 Para.1 enablement mandate and its implicit requirement of practical utility, or perhaps more accurately the underlying requirement of Section 101, to the facts of this case. As we have explained, the issue breaks down into two subsidiary issues: (1) whether a person of ordinary skill in the art would conclude that the applicants had sufficiently described particular diseases addressed by the invention, and (2) whether the Patent Act supports a requirement that makes human testing a prerequisite to patentability under the circumstances of this case.

The first subsidiary issue, whether the application adequately described particular diseases, calls for a judgment about what the various representations and discussions contained in the patent application's specification would say to a person of ordinary skill in

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the art. We have considered that question carefully, and, for the reasons we explained above in some detail, we conclude that the Board's judgment on this question was erroneous. Our conclusion rests on our understanding of what a person skilled in the art would gather from the various art cited, and from the statements in the application itself. We consider the Board's error to be sufficiently clear that it is reversible whether viewed as clear error or as resulting in an arbitrary and capricious decision.

The second subsidiary issue, whether human testing is a prerequisite to patentability, is a pure question of law: what does the practical utility requirement mean in a case of this kind. Under either our traditional standard or under the APA standard no deference is owed the Agency on a question of law, and none was accorded.

If the question concerning the standard of review, raised by the Commissioner, is to be addressed meaningfully, it must arise in a case in which the decision will turn on that question, and, recognizing this, the parties fully brief the issue. This is not that case. We conclude that it is not necessary to the disposition of this case to address the question raised by the Commissioner; accordingly, we decline the invitation to do so.

III. CONCLUSION

The Board erred in affirming the examiner's rejection under 35 U.S.C. Section 112 Para.1. The decision is reversed. *REVERSED* .

Footnotes

Footnote 1. Unless otherwise noted, all United States Code citations are to the 1988 edition.

Footnote 2. This is a divisional of patent application Serial No. 110,871 filed October 21, 1987.

Footnote 3. *In vivo* means " [i]n the living body, referring to a process occurring therein." *Steadman's Medical Dictionary* 798 (25th ed. 1990). *In vitro* means " [i]n an artificial environment, referring to a process or reaction occurring therein, as in a test tube or culture media." *Id.*

Footnote 4. The analysis in Paull consisted of grouping the previously-tested compounds into groups based on common structural features and cross- referencing the various groups, in light of the success rates of the group as a whole, to determine specific compounds that may be effective in treating tumors.

Footnote 5. *See supra* note 3.

Footnote 6. The specification does not state the specific type of human tumor cells used in this test.

Footnote 7. The chemical compound in Zee-Cheng *et al.* is labeled a 3,6-disubstituted-1,8-naphthalimide and uses different numbering for the positions on the isoquinoline ring. The structure of this compound, however, is identical to that claimed by the applicants except for symmetrical substitutions at the 5-position and the 8-position of the isoquinoline ring. Zee-Cheng *et al.* teaches identical substitutions of amino or nitro groups while applicants claim a nitro group substitution at the 5-position and an amino group substitution at the 8-position.

Footnote 8. HEp cells are derived from laryngeal cancer and HCT-29 cells from colon cancer.

Footnote 9. The examiner's answer noted that the final rejection also could have been made under 35 U.S.C. Section 101 for failure to disclose a practical utility.

Footnote 10. The examiner subsequently filed two supplemental answers in response to arguments raised by the applicants in supplemental reply briefs.

Footnote 11. *See, e.g., Cross v. Iizuka,* 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Langer,* 503 F.2d 1380, 183 USPQ 288 (CCPA 1974); *In re Krimmel,* 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *In re Bergel,* 292 F.2d 958, 130 USPQ 205 (CCPA 1961).

Footnote 12. This court's predecessor has determined that absence of utility can be the basis of a rejection under both 35 U.S.C. Section 101 and Section 112 Para.1. *In re Jolles,* 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche,* 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971) (" [I]f such compositions are in fact useless, appellant's specification cannot have taught how to use them."). Since the Board affirmed the examiner's rejection based solely on Section 112 Para.1, however, our review is limited only to whether the application complies with Section 112 Para.1.

Footnote 13. The Board's decision did not expressly make any independent factual determinations or legal conclusions. Rather, the Board stated that it "agree [d] with the examiner's well reasoned, well stated and fully supported by citation of relevant precedent position in every particular, and any further comment which we might add would be redundant." *Ex parte Brana et al.* , No. 92-1196 (Bd. Pat. App. & Int. March 19, 1993) at 2-3. Therefore, reference in this opinion to Board findings are actually arguments made by the examiner which have been expressly adopted by the Board.

Footnote 14. Paull also found NSC 308847 to be effective against two other test models, B16 melanoma and Colon C872.

Footnote 15. *See* Pazdur et al., *Correlation of Murine Antitumor Models in Predicting Clinical Drug Activity in Non-Small Cell Lung Cancer: A Six Year Experience,* 3 *Proceedings Am. Soc. Clin. Oncology* 219 (1984); Martin et al., *Role of Murine Tumor Models in Cancer Research,* 46 *Cancer Research* 2189 (April 1986).

Footnote 16. As noted, this would appear to be a Section 101 issue, rather than Section 112.

Footnote 17. *See also In re Novak,* 306 F.2d 924, 928, 134 USPQ 335, 337 (CCPA 1962) (stating that it is proper for the examiner to request evidence to substantiate an asserted utility unless one with ordinary skill in the art would accept the allegations as obviously valid and correct); *In re Chilowsky,* 229 F.2d 457, 462, 108 USPQ 321, 325 (CCPA 1956) (" [W]here the mode of operation alleged can be readily understood and conforms to the known laws of physics and chemistry . . . no further evidence is required."). *But see In re Marzocchi,* 439 F.2d at 223, 169 USPQ at 369-70 ("In the field of chemistry generally there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles.").

Footnote 18. *See supra* note 15.

Footnote 19. The declaration of Michael Kluge was signed and dated June 19, 1991. This declaration listed test results (i.e. antitumor activity) of the claimed compounds, *in vivo,* against L1210 tumor cells and concluded that these compounds would likely be clinically useful as anti-cancer agents. Enablement, or utility, is determined as of the application filing date. *In re Glass,* 492 F.2d 1228, 1232, 181 USPQ 31, 34 (CCPA 1974). The Kluge declaration, though dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. *In re Marzocchi,* 439 F.2d at 224 n.4, 169 USPQ at 370 n.4. It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility).

Footnote 20. We note that this discussion is relevant to the earlier discussion as well. If we were to conclude that these *in vivo* tests are insufficient to establish usefulness for the claimed compounds, that would bear on the issue of whether one skilled in the art would, in light of the structurally similar compounds in Paull and Zee Cheng *et al.* , have cause to doubt applicants' asserted usefulness for the compounds.

Footnote 21. Congress enacted the Administrative Procedure Act (APA) on June 11, 1946. *See* 1 *Kenneth Culp Davis, Administrative Law Treatise,* Section 1:7 (2d ed. 1978). The APA sets forth a framework for administrative agency procedure and provides judicial review for persons adversely affected by final agency actions. Chapter 7, codified at 5 U.S.C. Sections 701-706, contains the APA judicial review provisions, including the standard of review provision quoted above.

- End of Case -

In re Kirk and Petrow, 153 USPQ 48 (CCPA 1967)

In re Kirk and Petrow

(CCPA)
153 USPQ 48

Decided Mar. 16, 1967
Appl. No. 7522
U.S. Court of Customs and Patent Appeals

Headnotes

PATENTS

1. Specification - Sufficiency of disclosure (§ 62.7)

Specification does not comply with 35 U.S.C. 101 and 112 since nebulous expressions "biological activity" and "biological properties" do not contain a sufficiently explicit indication of usefulness of compounds and how to use them.

2. Specification - Sufficiency of disclosure (§ 62.7)

Congress intended 35 U.S.C. 112 to presuppose full satisfaction of requirements of section 101; necessarily, compliance with section 112 requires a description of how to use presently useful inventions; disclosure is insufficient where experimentation is necessary to determine actual uses, or possible lack of uses, of compounds, as well as how to employ them in a useful manner.

3. Patentability - Utility (§ 51.75)

Specification - Sufficiency of disclosure (§ 62.7)

It cannot be presumed that a steroid chemical compound is "useful" under 35 U.S.C. 101, or that one skilled in the art will know "how to use" it, simply because compound is closely related only in a structural sense to other steroid compounds known to be useful.

4. Patentability - Utility (§ 51.75)

Specification - Sufficiency of disclosure (§ 62.7)

Just as practical utility of compound produced by chemical process is essential element in establishing patentability of process, so the practical utility of compound produced by chemical intermediate, the starting material in such a process, is essential element in establishing patentability of intermediate; if process for producing product of only conjectural use is not itself useful within 35 U.S.C. 101, it cannot be said that starting materials for such a process, i.e., intermediates, are useful; it is not enough that specification disclose that intermediate exists and that it reacts, or can be used to produce intended product of no known use, nor is it enough that product disclosed to be obtained from intermediate belongs to some class of compounds which now is, or in the future might be, subject of research to determine some specific use; to extent that In re Nelson, 126 USPQ 242 , In re Wilke, 136 USPQ 435 , In re Adams, 137 USPQ 333 , and In re Szwarc, 138 USPQ 208 , are inconsistent with the above or with Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 , they are overruled.

Particular patents-Steroid Compounds

Kirk and Petrow, 1-Dehydro-6-Methyl Steroid Compounds, claims 11, 25, 26, 28, 29, 39, 41, and 45 of application refused.

Case History and Disposition:

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Appeal from Board of Appeals of the Patent Office.

Application for patent of David Neville Kirk and Vladimir Petrow, Serial No. 796,749, filed Mar. 3, 1959; Patent Office Group 120. From decision rejecting claims 11, 25, 26, 28, 29, 39, 41, and 45, applicants appeal. Affirmed; Rich and Smith, Judges, dissenting with opinions; Worley, Chief Judge, specially concurring with opinion.

See also 153 USPQ 266 .

Attorneys:
Bacon & Thomas (Jesse B. Grove, Jr., of counsel) both of Washington, D. C., for appellants.

Clarence W. Moore (Jack E. Armore of counsel) for Commissioner of Patents.

Judge:
Before Worley, Chief Judge, Rich, Smith, and Almond, Associate Judges, and Kirkpatrick, Judge. *

Opinion Text

Opinion By:
Worley, Chief Judge.

This appeal is from the decision of the Board of Appeals affirming the rejection of claims 11, 25, 26, 28, 29, 39, 41 and 45 in appellants' application [1] entitled "1-Dehydro-6-Methyl Steroid Compounds."

Each claim defines a specific steroid compound, claim 11 relating to a compound of the spirostane series; claims 25, 26, 28, 29 and 45 to compounds of the androstane series; and claims 39 and 41 to compounds of the pregnane series. It is unnecessary to reproduce any claim since the nature of the compounds will become apparent.

The Patent Office rejected all claims for failure of the specification "to comply with 35 U.S.C. 101 and 112." As we view the record, we are concerned with not only the legal adequacy of appellants' disclosure of "how to use" the claimed compounds under 35 U.S.C. 112, [2] but also the legal adequacy of assertions of usefulness in the original specification under 35 U.S.C. 101. [3] We

are particularly concerned with the applicability of the decision of the Supreme Court in Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 , to the facts here. [4]

The appropriate starting point for disposition of those issues is appellants' specification, which begins with several general statements as to how the claimed compounds are useful:

> It is an object of the present invention to provide a process for the conversion of 3-oxo-D D4-6-methyl and 3-oxo-D D4:6- 6-methyl steroidal derivatives into the corresponding 1-dehydro-derivatives which are a new class of compounds *often possessing high biological activity.*
>
> The present invention provides new 1-dehydro-derivatives of 3-oxo-D D4:6- 6-methyl and certain 3-oxo-D D4-6-methyl steroids having the formula
> *Tabular, graphic, or textual material set at this point is not available. Please consult hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.*
>
> (with or without a double bond at the 6:7 position) which 1-dehydro-derivatives are of value *on account of their biological properties* or *as intermediates in the preparation of compounds with useful biological properties* as herein indicated or as is apparent to those skilled in the art.
>
> The invention also provides the following new steroidal 6-methyl-1:4-dien-3-ones and 6-methyl-1:4:6-trien-3-ones which are of value *in steroid technology, in the furtherance of steroidal research and in the application of steroidal materials* to veterinary or medical practice, whether as tablets, elixirs, injections, implants, or other types of pharmaceutical preparation well known to those skilled in the art. (Emphasis supplied)

The description continues with lists of specific compounds of the cholestane, spirostane, androstane and pregnane steroid series together with a recital of "uses" for the compounds recited in the lists. Two compounds of the spirostane series are disclosed, one of which, 6-hydroxy-6-methyl-25D-spirosta - 1:4-dien-3-one, is the subject of claim 11. They are said to be

> * * * of value as *intermediates in the preparation of 6-methylated aromatic steroid hormones* into which intermediates they may be converted by reaction in solution in acetic anhydride with toluene-*p* -sulphonic acid. (Emphasis supplied)

Eighteen compounds of the androstane series are disclosed. The five recited in the claims are

> 17b-Hydroxy-6:17a - dimethyland-rosta-1:4:6-trien-3-one [Claim 45]
>
> 17a - Ethynyl-17b-hydroxy-6-methylandrosta-1:4:6-trien-3-one [Claim 25]
>
> 17b-Acetoxy-4:6a-dimethylandrosta-1:4-dien-3-one [Claim 26]
>
> 9a-Fluoro-11b:17b - dihydroxy-6a:17a-dimethylandrosta-1:4 - dien-3-one [Claim 28]
>
> 17b-Hydroxy - 6a-methyl-17a-(prop-l-ynyl) androsta - 1:4-dien-3-one [Claim 29]

They are said to be

> * * * of value *as intermediates in the preparation of 6-methylated aromatic steroidal hormones,* into which they may be converted by reaction in solution in acetic anhydride with toluene-r-sulphonic acid, *as intermediates in the preparation of biologically active compounds and in some cases on account of their biological properties.* (Emphasis supplied)

Some sixteen compounds of the pregnane series are disclosed, including the two compounds of claims 39 and 41,

> 6a-Methyl-16a:17a - *iso* propylidenedioxy - pregna - 1:4 - diene-3:20-dione [Claim 39] and
>
> 20:20 - Bisethylenedioxy - 6a-methyl-pregna-1:4 - dien-3-one [Claim 41].

They are alleged to be

> * * * of value *as intermediates in the preparation of compounds with valuable biological properties such as progestational properties or properties associated with the adrenocortical hormones or as intermediates in the preparation of compounds with useful biological properties.* (Emphasis supplied)

Appellants' arguments are, in the main, two-fold. They first contend that

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the specification is adequate to comply with § 101 and § 112 because it discloses that the claimed compounds "have present and useful biological activity of the nature known for analogous steroidal compounds," and that "one skilled in the art would know how to use the compounds of the claims to take advantage of their presently-existing biological activity." The second argument is that the specification adequately discloses that the compounds "have use as intermediates in the production of aromatic steroidal hormones and other biologically useful compounds," and that the examiner has admitted one skilled in the art would know how to use the claimed compounds as intermediates for that purpose. The respective arguments present somewhat different considerations, and will be discussed separately.

I. The Asserted "Therapeutic" or "Biological" Activity

In his final rejection, the examiner stated:

> All the claims are again rejected as lacking adequate utility. The disclosure fails to indicate to one skilled in the art how one is to use the novel compounds of this invention. The therapeutic properties are stated in such general terms i.e., "useful biological properties", that it fails to convey any useful information to one skilled in the art and further fails to state which of the claimed compounds have a therapeutic activity. * * *

In response, appellants submitted argument that the rejection "is not warranted," and also submitted an affidavit of one of the applicants, a Dr. Petrow, which appellants summarized in a letter accompanying the affidavit and substantially reiterate in their brief here:

> Attached hereto is an affirmation of Vladimir Petrow which shows that one skilled in the art would be able to determine the biological uses of the claimed compounds by routine tests. The Petrow affirmation specifically shows that * * * [the steroid of] (Claim 25) in the well-known McPhail modification of the Clauberg Assay possesses progestational activity on oral administration. The natural hormone, progesterone, on the other hand shows no response on oral administration in the same test. Accordingly, it is quite evident that the compound of claim 25 is a valuable oral progestational agent. This affirmation, accordingly, is proof of the fact that one skilled in the art would have no difficulty in determining whether *or not* the 1-dehydro derivatives of the pregnane series, as claimed, have value biologically as progestational agents. (Emphasis supplied)

> In addition, the Petrow affirmation * * * discloses the determination of the anabolic activity of * * * the compound of claim 26. It is shown by standard test procedure that this compound does have anabolic activity and that, in addition, it has a much higher anabolic/androgenic ratio than that of testosterone propionate, a well-known anabolic agent. * * *
>
> Further * * * the oral progestational activity of * * * the compound of claim 39, is set forth by virtue of *well-known test procedure.* This pregnane derivative is shown to be approximately 4 times as active progestationally on oral administration as * * * a well-known oral progestational agent. * * * by means of other tests the compound of claim 39 has been found to have valuable anti-inflammatory activity greater than that of either cortisone acetate or hydrocortisone. By virtue of a further standard test procedure the gluco corticoid activity of the compound of claim 39 has been shown to be more than 10 times that of cortisone and hydrocortisone acetates.
>
> The affirmation of Dr. Petrow not only shows that the compounds claimed do have biological activity as asserted in the specification, but that the nature of such biological activity can be readily determined by those skilled in the art by reason of standard test procedures. [5]

Appellants' affidavit and argument went for naught, the examiner responding that

> * * * the final rejection of all the claims in the case as lacking an adequate disclosure of utility is deemed sound and adhered to. * * *
>
> In his Answer before the board, the examiner rejected the claims.
>
> * * * as failing to comply with 35 U.S.C. 101 and 112 in that the specification fails to teach those skilled in the art how to use the invention. * * *

After reviewing the various passages

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of appellants' specification relating to the uses of the claimed compounds and "how to use" them, he concluded:

> * * * nowhere is there found a *specific* allegation of utility for any compound within the scope of the claims. Thus the specification does not describe the manner in such full, clear, concise and exact terms as to enable one skilled in the steroid art to use the compounds of the instant invention. * * * Appellants have not listed one specific use for their claimed steroids and as those skilled in the art know steroids are susceptible to hundreds of uses. *What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.* (Emphasis supplied)

With regard to the Petrow affidavit, the examiner stated:

> * * * it may be that oral progestational activity can be determined by procedures well known in the art. * * * Once one knows that a compound does have utility as a progestational agent, it is of course merely routine to determine at what doses this activity exists. In other words, if in the specification as filed there had been a specific allegation that the compounds herein claimed had progestational activity this would have been sufficient to satisfy 35 U.S.C. 112, since those skilled in the art would know how to use a steroid possessing progestational activity. Thus, the aforementioned affidavit is not determinative of the issue at bar which is if the specification as filed does not allege a specific utility would one skilled in the art know how to use the invention?

The board agreed, adding that the reference in the specification to "biological properties" of the claimed compounds "is so general and vague as to be meaningless." It found in the specification no reason to expect that any of the claimed compounds "presents the probability of usefulness in the same manner as a natural hormone."

Appellants rely on the allegations in their specification that the disclosed compounds have "biological activity" as adequate disclosure of a use for the claimed compounds, stating:

> The disclosure teaches that the novel compounds are, in some cases, of value because of their presently existing biological activity. The application * * * teaches that such *steroidal* materials may be applied to veterinary or medical practice in the form of tablets, elixirs, injections, implants or other pharmaceutical preparations. In other words, the compounds in question are to be used *in the manner of other steroid hormones* in veterinary or medical compositions.

They also rely on the Petrow affidavit as evidence of the proposition that one skilled in the art would know how to use the claimed compounds, and assert that "the Board erroneously, completely ignored the Petrow affirmation confirming present useful hormonal activity of some of the compounds * * *."

[1] We are not persuaded by appellants' arguments that their specification meets the requirements of §§ 101 and 112. It seems to us that the nebulous expressions "biological activity" or "biological properties" appearing in the specification convey no more explicit indication of the usefulness of the compounds and how to use them than did the equally obscure expression "useful for technical and pharmaceutical purposes" unsuccessfully relied upon by the appellant in In re Diedrich, 50 CCPA 1355, 318 F.2d 946, 138 USPQ 128 . [6]

Nor does the Petrow affidavit help appellants' cause here. While that affidavit may show that three of appellants' claimed compounds do *in fact* possess specific anabolic, anti-inflammatory or glucocorticoid activity or usefulness as oral progestational agents, that is not the issue before us. It is what the compounds are *disclosed* to do that is determinative here. In that regard, it is appropriate to note that the specification does not even intimate that the claimed compounds of the spirostane and pregnane series *themselves* have "biological activity," much less the specific progestational, glucocorticoid or anti-inflammatory activities mentioned in the affidavit. With respect to the eighteen androstanes that are disclosed, five of which are claimed here, it is said they "are of value * * * *in some cases* on account of their biological properties." (Emphasis supplied.) There is no suggestion *which* androstanes are of value for that reason, or *what* biological properties make them useful. [7]

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[2] Thus we agree with the solicitor that appellant's affidavit is simply an ex post facto affirmation irrelevant to the issue of adequacy of the original disclosure inasmuch as it attempts to add statements of usefulness to the disclosure of the application as filed. Indeed, the sum and substance of the affidavit appears to be that one of ordinary skill in the art would know "how to use" the compounds to find out in the first instance whether the compounds *are - or are not - in fact* useful or possess useful properties, and to ascertain what those properties are. It amounts to an admission that experimentation would be necessary to determine actual uses-or possible lack of uses-of the compounds, as well as how to employ them in a useful manner. But surely Congress intended § 112 to pre-suppose *full satisfaction* of the requirements of § 101. Necessarily, compliance with § 112 requires a description of how to use presently useful inventions, otherwise an applicant would anomalously be required to teach how to use a useless invention. As this court stated in Diedrich, quoting with approval from the decision of the board, 138 USPQ at 130:

> We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.

As the Supreme Court said in Brenner v. Manson, 148 USPQ at 696:

> * * * a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. * * *

Appellants further argue that the board had no grounds for concluding there was "no definite expectation from the specification" that any one of the claimed compounds "presents the probability of usefulness in the same manner as a natural hormone." According to appellants, "The analogy to known natural and synthetic hormones [presumably appellants intend to draw an analogy in chemical make-up or constitution between the claimed compounds and, for example, the natural hormone progesterone] enables one to predict that the new compounds would possess similar hormonal activity." Moreover, since some of the disclosed compounds of the pregnane series, not claimed here, were stated in the specification to be of value on account of their hydrocortisone-like anti-inflammatory properties, appellants contend that "it would not be unreasonable to predict that others of this series [i.e. the claimed pregnane derivatives] would also have this property."

[3] Similar arguments were advanced before, and rejected by, the Supreme Court in Brenner v. Manson, 383 U.S. at 531-2, 148 USPQ at 694. We find no error in the board's position on the facts of this case, absent a disclosure in the specification that the requisite properties of the *claimed* compounds are also similar to those of a natural or synthetic hormone of known activity. Appellants' arguments fail to recognize that many steroid compounds may possess no activity whatsoever. It cannot be presumed that a *steroid* chemical compound is "useful" under § 101, or that one of skill in the art will know "how to use" it, simply because the compound is closely related only in a structural sense to other steroid compounds known to be useful. Cf. In re Adams, 50 CCPA 1185, 316 F.2d 476, 137 USPQ 333 , dissenting opinion.

We conclude that appellants' specification does not comply with § 101 and § 112 merely on the statements of "biological" activity recited therein.

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II. The Asserted Usefulness as an "Intermediate"

As can be seen from the portions of the specification quoted earlier, appellants disclose that the claimed spirostane and androstane derivatives may be used as intermediates in the formation of 6-methyl aromatic steroids, and that the claimed pregnane derivatives may similarly be employed to produce steroids having "progestational properties" or "properties associated with the adreno-cortical hormones." [8]

The examiner has conceded that "those skilled in the art would know how to produce aromatic steroids" from the claimed compounds. However, he did not believe the inquiry into the adequacy of the disclosure should stop there, noting:

> * * * As to the portions of the disclosure which indicates that the claimed compounds are useful as intermediates in the production of 6-methylated aromatic steroids, *applicants have failed to show even one useful aromatic steroid which corresponds to the claimed intermediates. In other words, applicants' statement of utility is to the effect that the novel compounds claimed herein are useful in making other novel compounds which have no known use.* In the examiner's opinion this is not sufficient nor does the Examiner know of any decision holding that such a statement is adequate. (Emphasis supplied)

Appellants contend that the examiner's holding [9] "is straight into the teeth" of the decision of this court in In re Nelson, 47 CCPA 1031, 280 F.2d 172, 126 USPQ 242. They urge that the present disclosure with respect to the usefulness of the claimed compounds as intermediates "is on all fours" with that in Nelson. In their view, the examiner's requirement for disclosure of a use of the final products produced by carrying out the known process on the novel intermediates of the claims "is an absurdity" in view of Nelson and the further decisions of this court in In re Wilke, 50 CCPA 964, 314 F.2d 558, 136 USPQ 435; In re Adams; and In re Manson, 52 CCPA 739, 333 F.2d 234, 142 USPQ 35. They look upon the latter decisions as carrying forward the principle expressed in Nelson that, in their words, "there is no necessity for a specification to teach the use of an end product where such end product is not the invention claimed, but merely the result thereof."

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The decision in Nelson might well control here- *if* that decision were still a viable precedent. The question remains, however, whether the majority view in Nelson-that steroid chemical compounds may be useful under § 101 if they are useful to chemists doing research on steroids and can be used to produce steroids which are members of a general class some members of which are known to have useful therapeutic properties-can possibly remain the law in view of Brenner v. Manson.

There the Supreme Court, in considering what renders a process useful under § 101, discussed the cases cited by appellants here, stating (all emphasis supplied), 148 USPQ at 693-694:

> As is so often the case, however, a simple, everyday word [useful] can be pregnant with ambiguity when applied to the facts of life. That this is so is demonstrated by the *present conflict between the Patent Office and the CCPA* over how the test is to be applied to a chemical process which yields an already known product whose utility- *other than as a possible object of scientific inquiry* -has not yet been evidenced. It was not long ago that agency and court seemed of one mind on the question. In Application of Bremner, 37 CCPA 1032, 1034, 182 F.2d 216, 217, 86 USPQ 74, 75, the court affimed rejection by the Patent Office of both process and product claims. It noted that "no use for the products claimed to be developed by the processes had been shown in the specification." It held that "It was never intended that a patent be granted upon a product, or a process producing a product, unless such product be useful." Nor was this new doctrine in the court. See Thomas v. Michael, 35 CCPA 1036, 1038-1039, 166 F.2d 944, 946-947, 77 USPQ 216, 217-218.
>
> The Patent Office has remained steadfast in this view. The CCPA, however, has moved sharply away from Bremner. The trend began in Application of Nelson, 47 CCPA 1031, 280 F.2d 172, 126 USPQ 242. There, the court reversed the Patent Office's rejection of a claim on a process [product] yielding chemical intermediates "useful to chemists doing research on steroids," *despite the absence of evidence that any of the steroids thus ultimately produced were themselves "useful."* The *trend has accelerated,* [10] *culminating in* the present case where the court held it sufficient that a process produces the result intended and is not "detrimental to the public interest." 52 CCPA at 745, 333 F.2d at 238, 142 USPQ at 38.

Stripped of the highly technical procedural differences, the basic issue here, as in Brenner v. Manson, is whether the burden resting on an applicant to show that his invention is useful within the requirements of § 101 has been satisfied. While Manson did not disclose any use at all for the steroid compounds produced by his process, the arguments he advanced as to why those compounds were useful under § 101 correspond in substantial measure to the disclosure of the specification and the arguments relied on here. There can be no doubt that the insubstantial, superficial nature of vague, general disclosures or arguments of "useful in research" or "useful as building blocks of value to the researcher" was recognized, and clearly rejected, by the Supreme Court, 148 USPQ at 695-696:

> Whatever weight is attached to the value of encouraging disclosure and of inhibiting secrecy, *we believe a more compelling consideration is that a process patent in the chemical field, which has not been developed and pointed to the degree of specific utility,* creates a monopoly of knowledge which should be granted *only* if clearly commanded by the statute. * * * The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.
>
> *These arguments* for and against the patentability of a *process* which
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> Page 56
>
> either *has no known use* or is *useful only in the sense that it may be an object of scientific research* would *apply equally* to the patenting of the *product produced by the process.* Respondent appears to concede that with respect to a product, as opposed to a process, Congress has struck the balance on the side of nonpatentability unless "utility" is shown. Indeed, the decisions of the CCPA are in accord with the view that a product may not be patented absent a showing of utility greater than any adduced in the present case. *We find absolutely no warrant for the proposition that although Congress intended that no patent be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing,* a different set of rules was meant to apply to the process which yielded the unpatentable product. *That proposition seems to us little more than an attempt to evade the impact of the rules which concededly govern patentability of the product itself.* (Emphasis supplied)

[4] Wholly aside from the controlling impact of that reasoning here, the conclusion is inescapable that, just as the practical utility of the compound produced by a chemical process "is an essential element" in establishing patentability of the process, 383 U.S. 519, 148 USPQ 689 , so the practical utility of the compound, or compounds, produced from a chemical "intermediate," the "starting material" in such a process, is an essential element in establishing patentability of that intermediate. It seems clear that, if a process for producing a product of only conjectural use is not itself "useful" within § 101, it cannot be said that the starting materials for such a process-i.e., the presently claimed intermediates - are "useful." It is not enough that the specification disclose that the intermediate exists and that it "works," reacts, or can be used to produce some intended product of no known use. Nor is it enough that the product disclosed to be obtained from the intermediate belongs to some class of compounds which now is, or in the future might be, the subject of research to determine some specific use. [11] Cf. Reiners v. Mehltretter, 43 CCPA 1019, 1026, 236 F.2d 418, 421, 111 USPQ 97, 100, where compounds employed as intermediates to produce other *directly* useful compounds were found to be themselves useful.

It is impossible to reconcile the reasoning and conclusion of the majority in Nelson, Wilke, Adams and Szwarc with the majority view in Brenner v. Manson. Therefore, to the extent that those decisions are inconsistent with Brenner v. Manson and the views expressed herein, they must be, and are, overruled.

The decision is *affirmed.*

Footnotes

Footnote 1. Serial No. 796,749, filed March 3, 1959.

Footnote 2. 35 U.S.C. 112 reads in pertinent part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Footnote 3. 35 U.S.C. 101 reads in pertinent part:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or *composition of matter,* or any new and useful improvement thereof, may obtain a patent therefor, *subject to the conditions and requirements of this title.* (Emphasis supplied)

Footnote 4. This appeal was originally argued December 7, 1965, some three months prior to the decision in Brenner v. Manson on March 21, 1966. On November 10, 1966, this court restored the appeal to the calendar for reargument, and requested counsel to file memoranda "on the effect, if any, of Brenner v. Manson * * * on this appeal." Argument on that question was heard December 5, 1966.

Footnote 5. The record shows that the "standard test procedures" involved the use of laboratory animals, specifically rats and rabbits.

Footnote 6. There this court affirmed the rejection of certain claims for failure of an application to comply with section 112, noting that it had no " *specific* disclosure as to just *how* the compounds are to be *used.* "

Footnote 7. Appellants also rely on this court's decisions in In re Hitchings, 52 CCPA 1141, 342 F.2d 80, 144 USPQ 637 ; In re Dodson, 48 CCPA 1125, 292 F.2d 943, 130 USPQ 224 ; In re Krimmel, 48 CCPA 1116, 292 F.2d 948, 130 USPQ 215 ; and In re Bergel, 48 CCPA 1102, 292 F.2d 955, 130 USPQ 206 , for the proposition that usefulness of compositions of matter under § 101 may be established by an appropriate demonstration that the composition has useful properties or activities when tested in laboratory animals. Appellants correctly point out that the Supreme Court in Brenner v. Manson neither approved nor disapproved the reasoning and conclusions of those cases, 383 U.S. 531, 148 USPQ 694 . However, appellants' reliance on those cases here appears misplaced. In those cases, the inventors had carried their invention substantially further than appellants here, pharmacological testing having proceeded to an extent that some particular salutary effects on conditions inimical to animals could be ascribed to the compounds in issue there. The general results of those tests were disclosed in the application as filed, in contrast to the situation here. See also Archer v. Papa, 46 CCPA 835, 265 F.2d 954, 121 USPQ 413 ; Blicke v. Treves, 44 CCPA 753, 241 F.2d 718, 112 USPQ 472 .

Footnote 8. The disclosure with respect to the claimed pregnanes was characterized by the board as "even less helpful as to the manner in which these compounds may be used." We note, as did the solicitor, that appellants do not *disclose* either broadly or specifically what steroids having "progestational" or "adreno-cortical" properties may be produced from the claimed pregnanes. There is no hint in the disclosure as to what additional molecular substituents, if any, must be present in the steroids to be produced from the claimed pregnanes to obtain the recited properties. Nor do appellants direct our attention to *any* specific compound, possessing some specific property and known to the art at the time they filed their application, which can be prepared from the claimed pregnanes.

Footnote 9. It is interesting to compare the rejections voiced by the examiner and board and summarized by the solicitor in Nelson, 47 CCPA 1037-9, 280 F.2d 176-7, 126 USPQ 247 , with those raised here. For all intents and purposes, the rejections are identical. Although the board here found no decision "more directly relevant" than Nelson, nevertheless the examiner, board and solicitor all seek to distinguish it, urging that this court "evidently felt" that at least some of the products which could be made using Nelson's compounds as intermediates would be final products usable with no experimentation for specific therapeutic end purposes. The court did not intend Nelson to have the narrow scope attributed to it by the Patent Office. The most the court knew about what could be done with Nelson's C-19 14-hydroxy androstenes was that they could be used as intermediates to produce "steroids of a class at least some members of which are known to have useful therapeutic properties." The court took that as no guarantee that any of the *particular* "final

products" which might be produced from Nelson's *particular* intermediates themselves would have the cardiac glycoside activity of other members of the class. As appellants correctly note in their brief:

> In the Nelson case, one skilled in the art could not exactly predict what therapeutic properties the end products produced by the use of the claimed intermediates might have, nor could they predict that they would possess any at all. * * *

Appellants, however, also urge that their intermediates are "useful" substances even under the Patent Office interpretation of Nelson. They contend that the 6-methyl aromatic steroids produced from their claimed compounds *are* members of a class of aromatic estrogen compounds, some of which are useful commercially. They refer specifically to certain members of that class in their brief. But appellants have not disclosed or otherwise shown that *any* 6-methyl aromatic steroid which can be produced from their intermediates possesses activities in common with those commercial members of the aromatic steroid series. We cannot accept their arguments for reasons given under Part I of this opinion.

Footnote 10. In a footnote to the above comments, the Court added, 148 USPQ at 694:

> Thus, in Application of Wilke, 50 CCPA 964, 314 F.2d 558, 136 USPQ 435 , the court reversed a Patent Office denial of a process claim, holding that 35 U.S.C. § 112 (1964 ed.) was satisfied even though the specification recited only the manner in which the process was to be used and not any use for the products thereby yielded. See also Application of Adams, 50 CCPA 1185, 316 F.2d 476, 137 USPQ 333
>
> In Application of Szwarc, 50 CCPA 1571, 319 F.2d 277, 138 USPQ 208 , *the court acknowledged* that *its view of the law respecting utility of chemical processes had changed since Bremner.* * * * (Emphasis supplied)

Footnote 11. It does not appear that appellants seriously disagree with us on the matter, for in their memorandum on reargument they state:

> C. By analogy between a process for production of a product and an intermediate for producing an end product, such intermediate would not be useful within the meaning of 35 U.S.C. 101 merely because it can be used to make the intended product, or because the end product belongs to a class of compounds now the subject of serious scientific investigation.

Dissenting Opinion Text

Dissent By:
Rich, Judge.

Notice of Forthcoming Dissenting Opinion **

I, like Judge Smith, whose sentiments I share, am now revising a dissenting opinion to cover this case and the companion Joly case (No. 7472), 153 USPQ 45 , argued together December 5, 1966, and involving similar issues. I initially filed my tentative dissenting opinion herein February 1 in response to the December 22 majority opinion and a January 24 opinion in Joly. Thereafter the majority opinion in Joly was 75% rewritten on February 8 and again, on February 20, its content, responsive in part to observations in my dissent, was reduced 50%. In the ensuing three weeks the court has conferred on a long agenda of cases and held a week of hearings March 6-10, upon the conclusion of which I resumed, on March 13, my revision of the dissent. On that day notice was given by the Chief Judge that these two cases "will go down Thursday, March 16."

Protest to the arbitrary use of assumed power having proved futile, this unprecedented display of unseemly haste, condoned by the majority, necessitates this notice.

Footnotes

Footnote ** Editor's Note: See 153 USPQ 266 for dissenting opinions filed Apr. 10, 1967.

Dissenting Opinion Text

Dissent By:
Smith, Judge, dissenting.

Our usual practice is to release the majority opinion simultaneously with any dissenting opinions. There has been an unwarranted departure from this procedure in this case, the effect of which is to preclude an expression of my views at this time. I am unable to

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see wherein the cause of justice is served by such an irregular procedure. This dissent is therefore 1) a protest to the procedure here adopted, and 2) a notice that my full written dissent will be forthcoming as soon as the pressures of court work permit.

Concurring Opinion Text

Concur By:
Worley, Chief Judge, specially concurring.

It is most regrettable that for the first time in the history of this court, the usual orderly processes of the court have been ignored by a minority.

The instant appeal was *re-argued* December 5, 1966. The majority opinion was circulated December 22 in its present form. Yet, now, nearly three months later, the dissenting opinions are not available and no valid excuse is given.

It would seem that if the majority can direct its time and attention to expediting the work of the court it should not be too much to expect the same diligence from the minority.

It should not be necessary to say that the duty of this court is to the litigants, applicants for patents, the Patent Office and the public-not to the possible whims and caprices of individual judges. It is impossible to discharge that duty by condoning the instant derelictions, which hereafter will not be countenanced.

Footnote * Senior District Judge, Eastern District of Pennsylvania, sitting by designation.

- End of Case -

All Other Cases
Fiers v. Revel (CA FC) 25 USPQ2d 1601 (1/19/1993)

Fiers v. Revel (CA FC) 25 USPQ2d 1601

Fiers v. Revel

U.S. Court of Appeals Federal Circuit
25 USPQ2d 1601

Decided January 19, 1993
Nos. 92-1170, -1171

Headnotes

PATENTS

1. Patentability/Validity -- Date of invention -- Conception (§ 115.0403)

JUDICIAL PRACTICE AND PROCEDURE

Procedure -- Judicial review -- Standard of review -- Patents (§ 410.4607.09)

Conception is question of law, reviewed de novo on appeal, and if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until ▶reduction to practice◀ has occurred, that is, until after ▶gene◀ has been isolated; thus, regardless of complexity or simplicity of method of isolation employed, conception of DNA sequence, like conception of any chemical substance, requires definition of that substance other than by its functional utility.

PATENTS

2. Patentability/Validity -- Date of invention -- Conception (§ 115.0403)

Patent construction -- Claims -- Process (§ 125.1309)

Conception may occur if inventor is able to define DNA sequence by its method of preparation, but only if DNA is claimed by that method; conception of substance claimed per se, without reference to process, requires conception of its structure, name, formula, or definitive chemical or physical properties, and existence of workable method of preparation therefore cannot establish conception of subject matter of interference count in question, which is DNA sequence, having particular biological activity or function, claimed without reference to process.

3. Patentability/Validity -- Specification -- Written description (§ 115.1103)

JUDICIAL PRACTICE AND PROCEDURE

Procedure -- Judicial review -- Standard of review -- Patents (§ 410.4607.09)

Compliance with written description requirement of 35 USC 112 is question of fact, reviewed on appeal for clear error; interference party is entitled to benefit of earlier-filed foreign application only if specification satisfies description requirement by reasonably conveying to artisan that party had possession of claimed subject matter at time of application.

PATENTS

4. Practice and procedure in Patent and Trademark Office -- Interference -- Counts (§ 110.1703)

Patentability/Validity -- Specification -- Written description (§ 115.1103)

Specification containing statement that claimed DNA sequence is part of invention, and reference to potential method for isolating sequence, does not satisfy written description requirement of 35 USC 112, since specification does not describe DNA itself, nor even demonstrate that disclosed method would actually produce DNA in question, and since application therefore does not demonstrate that inventor had possession of claimed DNA; contention that correspondence between language of interference count and language in specification is sufficient to satisfy written description requirement is thus unpersuasive, since none of that language particularly describes DNA sequence in interference.

5. Practice and procedure in Patent and Trademark Office -- Interference -- Counts (§ 110.1703)

Patentability/Validity -- Date of invention -- Conception (§ 115.0403)

Patentability/Validity -- Specification -- Written description (§ 115.1103)

Disclosure sufficient to satisfy written description requirement of 35 USC 112 for claimed DNA sequence must have same degree of specificity as disclosure which demonstrates conception, and must therefore include precise definition of DNA, such as by structure, formula, chemical name, or physical properties; interference count at issue, which purports to cover all DNA sequences that code for particular interferon, is analogous to single means claim, which has been held not to comply with Section 112, and thus language claiming all DNA sequences which achieve particular result, without defining what means will do so, is not in compliance with description requirement, even if language corresponds to that of count.

6. Patentability/Validity -- Specification -- Enablement (§ 115.1105)

JUDICIAL PRACTICE AND PROCEDURE

Procedure -- Judicial review -- Standard of review -- Patents (§ 410.4607.09)

Enablement is question of law that is reviewed de novo on appeal; enablement requirement of 35 USC 112 is satisfied if application contains description that enables one skilled in art to make and use claimed invention.

PATENTS

7. Practice and procedure in Patent and Trademark Office -- Interference -- In general (§ 110.1701)

Practice and procedure in Patent and Trademark Office -- Interference -- Burden of proof (§ 110.1707)

Patentability/Validity -- Specification -- Enablement (§ 115.1105)

Prevailing party in interference that did not produce extrinsic evidence of enablement did not, thereby, fail to prove that application is enabling, since party asserting failure to comply with 35 USC 112 bears burden of persuasion on that issue, and since prevailing party therefore had no further burden to submit extrinsic evidence of enablement once examiner accepted sufficiency of specification; opposing party was not deprived of opportunity to challenge prevailing party's entitlement to Japanese application filing date, even if opposer had no opportunity to cross-examine due to prevailing party's election to stand on filing date, since opposing party had other opportunities, including during motion period, to make such challenge.

Case History and Disposition:

Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Three-way patent interference proceeding (no. 101,096), between Haruo Sugano, Masami Muramatsu, and Tadatsugu Taniguchi (application filed Oct. 27, 1980), Walter C. Fiers (application filed April 3, 1981), and Michel Revel and Pierre Tiollais (application filed Sept. 28, 1982). From decision awarding priority of invention (DNA which codes for a human fibroblast interferon-beta polypeptide) to Sugano, et al., Fiers and Revel, et al. appeal. Affirmed.

Attorneys:
David J. Lee, James F. Haley, Jr., and Ivor R. Elrifi, of Fish & Neave, New York, N.Y.; Roger L. Browdy, of Browdy & Neimark, Washington, D.C., for appellants.

Nels T. Lippert, of White & Case, New York, for appellees.

Judge:
Before Cowen, senior circuit judge, and Michel and Lourie, circuit judges.

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Opinion Text

Opinion By:
Lourie, J.

Walter C. Fiers, Michel Revel, and Pierre Tiollais appeal from the June 5, 1991 decision of the Patent and Trademark Office Board of Patent Appeals and Interferences, awarding priority of invention in a three-way interference proceeding, No. 101,096, to Haruo Sugano, Masami Muramatsu, and Tadatsugu Taniguchi (Sugano). We affirm.

BACKGROUND

This interference among three foreign inventive entities relates to the DNA 1 which

codes for human fibroblast beta-interferon (b-IF), a protein that promotes viral resistance in human tissue. It involves a single count which reads:

A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

The parties filed U.S. patent applications as follows: Sugano on October 27, 1980, Fiers on April 3, 1981, and Revel and Tiollais (Revel) on September 28, 1982. 2 Sugano claimed the benefit of his March 19, 1980 Japanese filing date, Revel claimed the benefit of his November 21, 1979 Israeli filing date, and Fiers sought to establish priority under 35 U.S.C. Section 102(g) based on prior conception coupled with diligence up to his British filing date on April 3, 1980.3

Sugano's Japanese application disclosed the complete nucleotide sequence of a DNA coding for b-IF and a method for isolating that DNA. 4 Revel's Israeli application disclosed a method for isolating a fragment of the DNA coding for b-IF as well as a method for isolating messenger RNA (mRNA) coding for b-IF, but did not disclose a complete DNA sequence coding for b-IF. 5 Fiers, who was working abroad, based his case for priority on an alleged conception either in September 1979 or in January 1980, when his ideas were brought into the United States, coupled with diligence toward a constructive reduction to practice on April 3, 1980, when he filed a British application disclosing the complete nucleotide sequence of a DNA coding for b-IF. According to Fiers, his conception of the DNA of the count occurred when two American scientists, Walter Gilbert and Phillip Sharp, to whom he revealed outside of the United States a proposed method for isolating DNA coding for b-IF, brought the protocol back to the United States. 6 Fiers submitted affidavits from Gilbert and Sharp averring that, based on Fiers' proposed protocol, one of ordinary skill in the art would have been able to isolate b-IF DNA without undue experimentation. 7 On February 26, 1980, Fiers' patent attorney brought into the United States a draft patent application disclosing Fiers' method, but not the nucleotide sequence for the DNA.

The Board awarded priority of invention to Sugano, concluding that (1) Sugano was entitled to the benefit of his March 19, 1980 Japanese filing date, 8 (2) Fiers was entitled to the benefit of his April 3, 1980 British filing date, but did not prove conception of the DNA of the count prior to that date, and (3) Revel was not entitled to the benefit of his November 21, 1979 Israeli filing date.

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The Board based its conclusions on the disclosure or failure to disclose the complete nucleotide sequence of a DNA coding for b-IF.

DISCUSSION *Fiers' Case for Priority*

The Board held that Fiers failed to establish conception in the United States prior to his April 3, 1980 British filing date. Specifically, the Board determined that Fiers' disclosure of a method for isolating the DNA of the count, along with expert testimony that his method would have enabled one of ordinary skill in the art to produce that DNA, did not establish conception, since "success was not assured or certain until the [b-IF] gene was in fact isolated and its sequence known." The Board relied on our opinion in *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991), in which we addressed the requirements necessary to establish conception of a purified DNA sequence coding for a specific protein. Accordingly, the Board held that Fiers was entitled only to the benefit of his April 3, 1980 British application date because only that application disclosed the complete nucleotide sequence of the DNA coding for b-IF. That date was subsequent to Sugano's March 1980 Japanese priority date.

Fiers argues that the Board erroneously determined that *Amgen* controls this case. According to Fiers, the Board incorrectly interpreted *Amgen* as establishing a rule that a DNA coding for a protein cannot be conceived until one knows the nucleotide sequence of that DNA. Fiers argues that this court decided *Amgen* on its particular facts and that this case is distinguishable. Fiers' position is that we intended to limit *Amgen* to cases in which isolation of a DNA was attended by serious difficulties such as those confronting the scientists searching for the DNA coding for erythropoietin (EPO), *e.g.*, screening a genomic DNA library with fully degenerate probes. According to Fiers, his method could have been easily carried out by one of ordinary skill in the art. 9 Fiers also argues that *Amgen* held that a conception of a DNA can occur if one defines it by its method of preparation. Fiers suggests that the standard for proving conception of a DNA by its method of preparation is essentially the same as that for proving that the method is enabling. Fiers thus urges us to conclude that since his method was enabling for the DNA of the count, he conceived it in the United States when Gilbert and Sharp entered the country with the knowledge of, and detailed notes concerning, Fiers' process for obtaining it.

[1] Conception is a question of law that we review *de novo*. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81, 87 (Fed. Cir. 1986) (citing *Barmag Barmer Maschinenfabrik AG v. Murata Machinery, Ltd.*, 731 F.2d 831, 837, 221 USPQ 561, 565 (Fed. Cir. 1984)). Although *Amgen* was the first case in which we discussed conception of a DNA sequence coding for a specific protein, we were not writing on a clean slate. We stated:

Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed chemical structure of the ▶gene◀ so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until ▶reduction to practice◀ has occurred, *i.e.*, until after the ▶gene◀ has been isolated.

927 F.2d at 1206, 18 USPQ2d at 1021. We thus determined that, irrespective of the complexity or simplicity of the method of isolation employed, conception of a DNA, like conception of any chemical substance, requires a definition of that substance other than by its functional utility.

[2] Fiers' attempt to distinguish *Amgen* therefore is incorrect. We also reject Fiers' argument that the existence of a workable method for preparing a DNA establishes conception of that material. Our statement in *Amgen* that conception may occur, *inter alia,* when one is able to define a chemical by its method of preparation requires that the

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DNA be claimed by its method of preparation. We recognized that, in addition to being claimable by structure or physical properties, a chemical material can be claimed by means of a process. A product-by-process claim normally is an after-the-fact definition, used after one has obtained a material by a particular process. Before reduction to practice, conception only of a process for making a substance, without a conception of a structural or equivalent definition of that substance, can at most constitute a conception of the substance claimed as a process. Conception of a substance claimed *per se* without reference to a process requires conception of its structure, name, formula, or definitive chemical or physical properties.

The present count is to a product, a DNA which codes for b-IF; it is a claim to a product having a particular biological activity or function, and in *Amgen,* we held that such a product is not conceived until one can define it other than by its biological activity or function. The difficulty that would arise if we were to hold that a conception occurs when one has only the idea of a compound, defining it by its hoped-for function, is that would-be inventors would file patent applications before they had made their inventions and before they could describe them. That is not consistent with the statute or the policy behind the statute, which is to promote disclosure of inventions, not of research plans. While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity.

Fiers has devoted a considerable portion of his briefs to arguing that his method was enabling. The issue here, however, is conception of the DNA of the count, not enablement. Enablement concerns teaching one of ordinary skill in the art how to practice the claimed invention. *See* 35 U.S.C. Section 112 (1988); *Amgen,* 927 F.2d at 1212, 18 USPQ2d at 1026. Since Fiers seeks to establish priority under section 102(g), the controlling issue here is whether he conceived a DNA coding for b-IF, not whether his method was enabling.

We conclude that the Board correctly decided that conception of the DNA of the count did not occur upon conception of a method for obtaining it. Fiers is entitled only to the benefit of his April 3, 1980 British filing date, since he did not conceive the DNA of the count under section 102(g) prior to that date.

Revel's Case for Priority

Revel bears the burden of proving entitlement to the benefit of his earlier-filed Israeli application date. *Utter v. Hiraga,* 845 F.2d 993, 998, 6 USPQ2d 1709, 1713 (Fed. Cir. 1988). To meet this burden, Revel must prove that his application meets the requirements of 35 U.S.C. Section 112, first paragraph, *Bigham v. Godtfredsen,* 857 F.2d 1415, 1417, 8 USPQ2d 1266, 1268 (Fed. Cir. 1988) (citing *Cross v. Iuzika,* 753 F.2d 1040, 1043, 224 USPQ 739, 741 (Fed. Cir. 1985)), which provides in pertinent part:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same. . . .

Revel thus must show that the Israeli application contains a written description of the DNA of the count and that it is enabling.

The Board held that Revel's Israeli application did not contain a written description of a DNA coding for b-IF since it did not disclose the nucleotide sequence or "an intact complete gene." The Board, in denying Revel's request for reconsideration, rejected the argument that it is only necessary to show some correspondence between the language in the count and language in the Israeli application to satisfy the written description requirement. The Board stated:

Moreover, what is needed to meet the description requirement will necessarily vary depending on the nature of the invention claimed. The test for sufficiency of support is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." As is apparent from our decision, we found the description in Revel's Israeli application inadequate to reasonably convey to the artisan that Revel was in possession of the invention of beta-interferon DNA [citations omitted].

Relying on *Amgen,* the Board concluded that the Israeli application was not enabling since Revel had not yet conceived the DNA of the count and " [l]ogically, one cannot . . . enable an invention that has not been conceived." Slip op. at 13.

Revel argues that the disclosure of his Israeli application satisfies the written description requirement because it contains language of similar scope and wording to that of the count. Revel cites the following passages from the Israeli application:

The invention thus concerns also said purified m-RNAs which comprises normally up to 900-1000 nucleotides. . . . In the

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same manner *it also concerns the corresponding c-DNA which can be obtained by transcription of said RNAs* [emphasis added]; It is a further object of the present invention to provide a process for the isolation of genetic material (DNA) containing the nucleotide sequence coding for interferon in human cells.

Revel points to a claim in the original Israeli application that corresponds substantially to the language of the count. 10 According to Revel, since the language of the count refers to a DNA and not to a specific sequence, the specification need not describe the sequence of the DNA in order to satisfy the written description requirement. Revel thus urges that only similar language in the specification or original claims is necessary to satisfy the written description requirement.

[3] We disagree. Compliance with the written description requirement is a question of fact which we review for clear error. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991); *Utter*, 845 F.2d at 998, 6 USPQ2d at 1714. On reconsideration, the Board correctly set forth the legal standard for sufficiency of description: the specification of Revel's Israeli application must "reasonably convey [ ] to the artisan that the inventor had possession at that time of the . . . claimed subject matter." Slip op. at 3 (citing *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1117).

[4] An adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. Revel's specification does not do that. Revel's application does not even demonstrate that the disclosed method actually leads to the DNA, and thus that he had possession of the invention, since it only discloses a clone that might be used to obtain *mRNA* coding for b-IF. 11 A bare reference to a DNA with a statement that it can be obtained by reverse transcription is not a description; it does not indicate that Revel was in possession of the DNA. Revel's argument that correspondence between the language of the count and language in the specification is sufficient to satisfy the written description requirement is unpersuasive when none of that language particularly describes the DNA.

[5] As we stated in *Amgen* and reaffirmed above, such a disclosure just represents a wish, or arguably a plan, for obtaining the DNA. If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, as we have held, then a description also requires that degree of specificity. To paraphrase the Board, one cannot describe what one has not conceived.

Because the count at issue purports to cover all DNAs that code for b-IF, it is also analogous to a single means claim, which has been held not to comply with the first paragraph of section 112. *See In re Hyatt*, 708 F.2d 712, 218 USPQ 195, 197 (Fed. Cir. 1983) ("the enabling disclosure of the specification [must] be commensurate in scope with the claim under consideration.") Claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement; it is an attempt to preempt the future before it has arrived.

The Board's determination that the Israeli application does not contain a written description of a DNA coding for b-IF was thus not clearly erroneous. The Board correctly determined that Revel is not entitled to the benefit of his November 1979 Israeli application since it fails to satisfy the written description requirement of section 112.12

Sugano's Case for Priority

The Board held that Sugano established entitlement to his March 19, 1980 Japanese filing date because the disclosure of his Japanese application contains the complete and correct sequence of the DNA which codes for b-IF, along with a detailed disclosure of the method used by Sugano to obtain that DNA. The Board rejected Fiers' argument that Sugano's March 1980 application is not enabling, since Fiers presented only attorney argument that was "unsupported by competent

evidence, entitled to little or no weight and [was] unpersuasive in any event." Slip op. at 12.

Fiers argues that Sugano failed to prove that his application is enabling because he did not produce extrinsic evidence showing enablement. Fiers also argues that the Board erroneously imposed a burden on him to show that Sugano's application is not enabling when, in fact, Fiers had no right to submit rebuttal evidence once Sugano elected to rely solely on his Japanese application.

[6] [7] Enablement is a question of law that we review *de novo*. *Amgen*, 927 F.2d at 1212, 18 USPQ2d at 1026. Enablement requires that the application " 'contain a description that enables one skilled in the art to make and use the claimed invention.' " *Id.*, (citing *Atlas Powder Co. v. E.I. duPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984)). " [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of Section 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). " [A]ny party making the assertion that a U.S. patent specification or claims fails, for one reason or another, to comply with Section 112 bears the burden of persuasion in showing said lack of compliance." *Weil v. Fritz*, 601 F.2d 551, 555, 202 USPQ 447, 450 (CCPA 1979). Thus, once the examiner accepted the sufficiency of Sugano's specification, Sugano had no further burden to prove by extrinsic evidence that his application was enabling; the Board correctly determined that it was Fiers (or Revel) who then had to prove that Sugano's application was not enabling. Even if Fiers had no opportunity to cross-examine Sugano because Sugano elected to stand on his filing date, Fiers had other opportunities, including during the motion period, to challenge Sugano's entitlement to his Japanese application filing date. Thus, he did not lack opportunity to challenge.

We conclude that Sugano is entitled to rely on his disclosure as enabling since it sets forth a detailed teaching of a method for obtaining a DNA coding for b-IF and the Board did not err in determining that Fiers presented no convincing evidence impeaching the truth of the statements in Sugano's patent specification. We also conclude that Sugano's application satisfies the written description requirement since it sets forth the complete and correct nucleotide sequence of a DNA coding for b-IF and thus "convey [s] with reasonable clarity to those skilled in the art that, as of the filing date sought, [Sugano] was in possession of the [DNA coding for b-IF]." *See Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1117. The Board correctly determined that Sugano's March 19, 1980 Japanese application satisfies the requirements of section 112, first paragraph, and that Sugano thus met his burden to establish entitlement to that filing date.

CONCLUSION

The Board correctly awarded priority of invention to Sugano. Accordingly, the decision of the Board is

AFFIRMED.

Footnotes

Footnote 1. DNA is deoxyribonucleic acid, a generic term encompassing the many chemical materials that genetically control the structure and metabolism of living things.

Footnote 2. Revel assigned his application to Yeda Research and Dev. Co. Ltd. The real party in interest in the Fiers application has been indicated to be Biogen, Inc. The real party in interest in the Sugano application has been indicated to be Juridical Foundation, Japanese Foundation for Cancer Research.

Footnote 3. 35 U.S.C. Section 102 provides in pertinent part:

A person shall be entitled to a patent unless . . .

(g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Footnote 4. Sugano's method involved the preparation of two populations of radioactivity-labelled cDNA probes prepared from the mRNA of fibroblast cells. One population of probes was prepared from the mRNA of induced fibroblast cells and the other population from the mRNA of non-induced cells. These probes were then exposed to a cDNA library prepared from induced cells, and the clones that only hybridized with the first probe were selected. The selected clones were then used as probes to select the full-length DNA sequence encoding b-IF, which was then sequenced.

Footnote 5. Revel's method involved preparing a cDNA library of clones from the mRNA of cells induced to produce b-IF, screening each clone for hybridization to mRNA from induced cells, eluting the hybridized mRNA, and assaying the eluted mRNAs for b-IF activity.

Footnote 6. Fiers presented his protocols and progress to date toward isolating DNA coding for b-IF at a September 21, 1979 meeting in Paris at which Sharp and Gilbert were present. Sharp and Gilbert returned to the United States on September 23 and 24, respectively. Fiers made a second presentation in Martinique on January 12, 1980. Gilbert and Sharp were both present and returned to the United States on January 15 and 17, respectively. On March 25, 1980, Fiers disclosed by telephone to his patent attorney that he had determined the entire nucleotide sequence of a DNA coding for b-IF. Fiers presented that nucleotide sequence along with a protocol for preparing the complete DNA in Switzerland on March 28, 1980. Fiers and his attorney worked from March 31 until April 2 in Ghent drafting the final portion and claims of the British application that Fiers filed on April 3, 1980.

Footnote 7. Fiers' proposed protocol involved preparing a cDNA library from the mRNA of cells induced to produce b-IF mRNA, and screening the cDNA library for a cDNA that, when introduced into a cell, would cause it to display b-IF activity.

Footnote 8. Sugano also claimed the benefit of an October 30, 1979 Japanese filing date which the Board denied. Sugano does not challenge that determination on appeal.

Footnote 9. Fiers' method involved screening a cDNA library which he maintains is smaller and less complex than a genomic DNA library. Fiers also contends that his screening techniques were routine to those skilled in the art, while those skilled in the art lacked experience screening with fully degenerate probes. Fiers also notes that, in contrast to the situation with EPO in which erroneous amino acid sequence information had been published, the first thirteen amino acids of b-IF were known to the art.

Footnote 10. Claim 22 of Revel's original Israeli application reads:

The DNA coding for a polypeptide having interferon activity insertable in a vector, such as plasmid PBR-322, and having up to 900-1000 nucleotides.

Footnote 11. According to Fiers, Revel's Israeli application also fails the written description requirement because the mRNA disclosed in the application encodes a protein weighing 23,000 daltons which is interleukin-6, not b-IF. The Board did not premise its decision on this point, and, since we determine that Revel's application does not describe the DNA of the count, we need not reach it either.

Footnote 12. In light of our disposition of the written description requirement question, we do not address whether Revel's Israeli application satisfies the enablement requirement.

- End of Case -